

1 UNITED STATES DISTRICT COURT
2 NORTHERN DISTRICT OF WEST VIRGINIA

3 Biogen International GMBH
4 and Biogen MA, Inc.,

5 Plaintiffs,

6 vs. CIVIL ACTION NO.

7 1:17-cv-116

8 Mylan Pharmaceuticals, VOLUME I
9 Inc.,

10 Defendant.

11 - - -

12 TRANSCRIPT

13 of proceedings had in the bench trial of the
14 above-styled action on February 4, 2020, before Honorable Irene
15 M. Keeley, District Judge, at Clarksburg, West Virginia.

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1 Tuesday Morning Session,

2 February 4, 2020, 9:30 a.m.

3 - - -

4 THE COURT: Thank you. Good morning. It's been so
5 many years since I've been down here, I didn't know what I was
6 doing this morning. Didn't know where the parking lot was,
7 thought there was a secured entrance and there wasn't. And so,
8 anyway, it's good to be here with you all.

9 And has there been any -- I know we have an updated
10 witness list, but is there anything that we need to take up
11 before opening statements?

12 MR. ANSTAETT: Your Honor, David Anstaett of Perkins
13 Coie on behalf of Mylan Pharmaceuticals. We did have one issue
14 we would like to raise with the Court. Our understanding is
15 that Biogen has two fact witnesses in the case, and we would
16 like to request that those fact witnesses be sequestered aside
17 from when they are testifying.

18 THE COURT: If there are any fact witnesses on either
19 side in the courtroom, the rule has been invoked and you must
20 leave at this time and await the time when you're called to
21 testify.

22 Are they in the courtroom?

23 MR. MONROE: I don't believe they are, Your Honor.

24 THE COURT: That's fine. That takes care of that
25 one. And are there any other issues?

1 MR. MONROE: Yes, Your Honor. We just wanted to
2 remind the Court that the parallel proceeding in the patent
3 office, the IPR proceeding --

4 THE COURT: February 6.

5 MR. MONROE: Correct. Decision could come down any
6 moment.

7 THE COURT: We may get a ruling from them before Iowa
8 gets a ruling.

9 MR. MONROE: Based on patent office procedures, it is
10 very possible it could come down as we're speaking to you this
11 morning. So we just wanted to alert the Court to that and, if
12 that were to happen, ask if we could have a recess so that we
13 could review the decision and meet and confer to talk about
14 potential impact on the proceedings.

15 THE COURT: No problem. Certainly. No problem at
16 all.

17 Anything else?

18 MR. MONROE: No, Your Honor.

19 THE COURT: In that case, how do you wish to proceed?
20 I know we have burdens and all here. Who wants to open?

21 MR. ANSTAETT: So, Your Honor, I believe we will open
22 first, and I will do that. I don't know if you would like to
23 hear formal appearances. Mr. Copland was going to introduce
24 folks.

25 MR. COPLAND: Yes, Your Honor. Good morning. As you

1 know, I'm Gordon Copland appearing for Mylan.

2 THE COURT: I was just afraid all the appearances
3 might take 15 minutes.

4 MR. COPLAND: For today, Your Honor, it will be David
5 Anstaett, Shannon Bloodworth, and Courtney Prochnow.

6 THE COURT: And for Biogen?

7 MS. LAW: Your Honor, Sandra Law and James Monroe,
8 Paul Browning, and Li Feng.

9 THE COURT: Thank you very much. You may proceed.

10 MR. MONROE: Your Honor, we do have hard copies of
11 the slides to pass out, if that would be acceptable.

12 THE COURT: That will be fine.

13 MR. MONROE: We were attempting to avoid interrupting
14 at the very beginning of the trial. We would like to note
15 there appears to be a disagreement with respect to obligations
16 to provide demonstratives in advance of the opening and also
17 the witnesses.

18 We received a set of opening demonstratives from
19 defendants yesterday that were numbered up to 49, but we only
20 got 35 pages. So we asked what are those other pages, and they
21 said they're just blowups that they were going to show over the
22 exhibits.

23 What we're seeing now in this set of slides is they
24 actually have titles and they're nice things they're presenting
25 to you in a packet that we did not see. And that's also

1 particularly problematic for their first witness because we
2 received a set of slides, 111 slides, numbered to 111, but we
3 only received 58 slides.

4 So we assume, for the next witness, we're going to
5 get a huge number of slides or Your Honor will get a packet
6 with titles set up, blowouts we've never had an opportunity to
7 review.

8 THE COURT: Well, it's a firm rule that they have to
9 have an opportunity to review them.

10 MR. ANSTAETT: I can respond to that, Your Honor.
11 Let me give you an example. If you'll look in your -- what I
12 just handed up. If you look at, for example, Slide 7, there's
13 a title there that says "Kolbach 1992."

14 THE COURT: Slide 7 is the last number? The last
15 number in the DDX would be 7?

16 MR. ANSTAETT: Precisely.

17 THE COURT: I'm there.

18 MR. ANSTAETT: So, as you can see, that's simply a
19 blowup of the demonstrative of an article. The title is not
20 descriptive or argumentative; it just gives the name of the
21 author and the year.

22 And the pretrial order which I have here says as
23 follows:

24 "A party will provide demonstrative exhibits to be
25 used in connection with direct examination by 6:00 p.m. the

1 night before their intended use, and objections will be
2 provided no later than 7:30 p.m. the night before their
3 intended use. Parties shall meet and confer by 8:30 p.m. the
4 night before their intended use."

5 Then in paragraph 25 it says this:

6 "These provisions do not apply to demonstratives
7 intended for use in closing statements, created during
8 testimony, or demonstratives to be used for cross-examination,
9 none of which need to be provided to the other side in advance
10 of their use."

11 And here's the key part:

12 "In addition, blowups or highlights of exhibits or
13 parts of exhibits or testimony are not required to be provided
14 to the other side in advance of their use. Moreover, slides
15 that constitute only blowups or highlights of exhibits are not
16 required to be provided to the other side in advance of their
17 use."

18 And so this is precisely what's contemplated by the
19 pretrial order in this case.

20 THE COURT: But I do believe that, during the -- at
21 the conclusion of the pretrial conference, I did state that I
22 expected the parties to exchange any demonstratives they were
23 going to use in opening statements.

24 MR. ANSTAETT: And we did. I mean, I understand
25 that, Your Honor. We relied on that language in the pretrial

1 order. And again --

2 THE COURT: So wait a minute. What was my statement
3 on record during the final pretrial conference?

4 MR. ANSTAETT: I fully acknowledge that that was --

5 THE COURT: Hot air, I guess?

6 MR. ANSTAETT: I'm sorry.

7 THE COURT: Hot air?

8 MR. ANSTAETT: Oh, of course not, Your Honor.

9 THE COURT: Okay. Well, then, why didn't you do it?

10 MR. ANSTAETT: Because, Your Honor, we didn't think
11 what you said was inconsistent with the pretrial order. And,
12 frankly, I think, as we go through these, there will be no
13 dispute whatsoever that these are simply blowups, as explicitly
14 stated in the pretrial order, of exhibits that we intend to
15 use.

16 THE COURT: The local rules of this court indicate
17 that a judge may, at his or her discretion, modify the local
18 rules. And everything that I said with regard to the exchange
19 of exhibits is based on my experience of a blood war over "I
20 didn't see Exhibit 14; you gave me 13," which is what is
21 happening this morning, which is why "all" is of some
22 significance.

23 Now the question is is there any way in which Biogen
24 would be prejudiced? And I think the answer is probably not,
25 if not no.

1 MR. MONROE: Your Honor, I think two issues. One,
2 I'd like to point out that, with respect to the concept of
3 these are just blowups, a lot of the slides that we were
4 provided last night were also blowups. So they selectively
5 chose -- for example, Slide 13 in your binder shows a blowup
6 out of a document. But then Slides 14 and 15, we didn't get,
7 which show blowups. So there wasn't really a consistent -- we
8 raised the issue, and they did not say this is --

9 THE COURT: Wait a minute. Slide 14, Kappos 2005
10 poster, even I know what this is. It's not a surprise.

11 MR. MONROE: We haven't had a chance to go through
12 all the slides yet, Your Honor. I'm trying to provide these
13 quickly. Slide 15, for example, they're doing blowups.

14 My point is they did blowups for other documents, but
15 then for others they didn't provide us with those blowups.

16 And I think for the opening, I would agree with Your
17 Honor. I think we're going to be fine for the opening. This
18 is not evidence per se.

19 THE COURT: Well, it's not evidence.

20 MR. MONROE: We're concerned that they are providing
21 you with a packet they haven't seen.

22 THE COURT: They won't do it again.

23 MR. MONROE: Our concern is for the first witness --

24 THE COURT: For both sides going forward -- sorry to
25 override you, but I need to move this forward -- all exhibits

1 that you intend to use the following day. A-L-L. Look it up
2 in Webster's. It means everything. And that's what I want to
3 be exchanged by both sides. Okay?

4 MR. MONROE: Could I ask for one thing, Your Honor,
5 which is --

6 THE COURT: Don't push.

7 MR. MONROE: I'm hoping this isn't pushing.
8 Dr. Greenberg is their first witness, Your Honor, and their
9 only witness in their case in chief, and they clearly have 111
10 slides, and there's only 58 -- they didn't give 58 of those.

11 Can they provide them now so we can be looking at
12 them in advance of this?

13 MR. ANSTAETT: Yes, absolutely.

14 THE COURT: Why don't each of you designate one
15 lawyer to provide it to the other lawyer. That way nobody will
16 be wondering who's preparing to provide those and who's to
17 receive them.

18 So who will provide them?

19 MR. ANSTAETT: For our side, we will designate
20 Ms. Greb to play that role, Your Honor.

21 THE COURT: Ms. Greb.

22 And who will receive them for Biogen?

23 MR. MONROE: Mark Feldstein, Your Honor. We now have
24 it. They have now provided it to Mr. Feldstein.

25 Just to confirm so there's no confusion, consistent

1 with the rules, this would be simply our affirmative
2 demonstratives, not cross-examination items that we might use,
3 blowups of cross-examination documents and things like that.

4 THE COURT: I'm sorry. Was that a question?

5 MR. MONROE: Yes.

6 THE COURT: And you want -- you want to make sure
7 that you don't have to provide your documents that are used for
8 impeachment purposes only?

9 MR. MONROE: Correct. And they don't either, either
10 party.

11 THE COURT: Right. But to the extent you try to get
12 in a document, get it into evidence with someone on
13 cross-examination, that's a different kettle of fish. Okay?
14 For impeachment purposes only, you do not have to provide that.
15 Neither side does. But anything substantive that you would
16 say, "Well, Judge, this witness is here. In the effort to be
17 expeditious and reasonable, we want to move this into
18 evidence," and the other side said, "Oh, it's not
19 cross-examination, and we haven't seen it," I do not want that
20 scenario. Okay?

21 So just by way of a basis point for all of you to
22 understand, I am an old trial lawyer and an old trial judge.
23 Okay? And it seems to me that, after a lot of years of
24 experience, the best way to move this thing forward is to have
25 as little fighting between the sides. I don't want a Battle of

1 the Somme over this, and I want you to cooperate; because,
2 otherwise, I will have to intervene, and neither side's going
3 to be happy with that.

4 So reasonableness and efficiency and cooperation
5 would be the hallmarks as far as I'm concerned here. Okay?
6 And if you -- I think, if you can proceed in that manner, even
7 if it may violate somebody's sensibilities about the -- this is
8 not exactly what the words in the pretrial order or the local
9 rules say, we'll all get along better. Okay?

10 MR. ANSTAETT: Understood, Your Honor. Thank you
11 very much.

12 THE COURT: Appreciate it.

13 MR. ANSTAETT: Good morning, Your Honor. As I said,
14 my name is David Anstaett and, together with my colleagues, we
15 represent Mylan Pharmaceuticals.

16 This case involves a single patent and presents two
17 core questions. First, whether the asserted claims of the '514
18 patent are obvious. And, second, does the '514 patent satisfy
19 the written description and enablement requirements?

20 And the answers are that the patent is obvious and,
21 if not, if not, then it entirely fails to satisfy the written
22 description and enablement requirements.

23 Now, the '514 patent has narrow claims directed to a
24 specific dose of a specific drug to treat a specific disease.
25 And they recite nothing more than what skilled artisans would

1 readily arrive at through routine optimization in view of the
2 substantial prior art. And, if the numerous disclosures in the
3 prior art somehow would not have rendered the claims obvious,
4 then there is nothing in the patent specifications that could
5 satisfy the written description and enablement requirements.

6 So let's start with the '514 patent. It has
7 essentially three elements. It claims a method of treating
8 multiple sclerosis with a therapeutically effective amount of
9 dimethyl fumarate where that therapeutically effective amount
10 is about 480 milligrams per day.

11 And the first issue is whether the treatment method
12 recited in the '514 patent would have been obvious to skilled
13 artisans at the priority date in February of 2007. The
14 evidence will show it was, indeed, obvious.

15 So let's start with dimethyl fumarate or DMF, as the
16 parties will call it throughout the case.

17 There's no dispute that DMF was a well-known compound
18 at the priority date. It was in the prior art at the priority
19 date. The '514 patent is not a composition patent. Biogen
20 does not claim to have discovered dimethyl fumarate. Dimethyl
21 fumarate was well known in the prior art.

22 I think there's also no real dispute that it was well
23 known in the prior art before the priority date that dimethyl
24 fumarate was effective for treating multiple sclerosis.

25 By the priority date, DMF had been successfully used

1 in at least two clinical trials to treat patients with multiple
2 sclerosis, and its use had even been claimed in prior art
3 patents for exactly that purpose. And we see that here.

4 These are Claims 1 and 2 of the '376 patent, which
5 claim dimethyl fumarate for the therapy of autoimmune diseases,
6 such as multiple sclerosis. And this is one of the patents
7 that was originally asserted by Biogen against Mylan in this
8 case, but it has now expired. And it's prior art to the '514
9 patent.

10 This is the '999 patent, another patent originally
11 asserted against Mylan in this case, and it too has expired.
12 And, as you can see, it's titled "Dimethyl fumarate for the
13 treatment of multiple sclerosis," and it was filed in July
14 2002, years before the priority date of the '514 patent.

15 So treating patients with -- MS patients with DMF was
16 known in the prior art, and it was patented.

17 So that just leaves the therapeutically effective
18 dose of about 480 milligrams per day. And here too the prior
19 art disclosed an effective dose range running from
20 360 milligrams to 720 milligrams per day administered in three
21 equal doses taken throughout the day. And precisely
22 480 milligrams of dimethyl fumarate per day had successfully
23 been used in the prior art to treat psoriasis. And, like MS,
24 psoriasis is an autoimmune disease, and it has an immunological
25 pathway that is similar to MS.

1 Now, at the priority date it was also well known that
2 DMF caused certain unpleasant side effects, including
3 gastrointestinal side effects. And given basic drug
4 development principles at a likely effective dose range in MS
5 disclosed in the prior art, skilled artisans would have been
6 motivated to find the minimum effective dose of DMF to treat MS
7 using routine optimization, both to minimize side effects and
8 because lowered dosing allowed twice-a-day dosing rather than
9 three-times-a-day dosing, and that would improve patient
10 compliance and patient convenience.

11 480 milligrams was an obvious choice for dosing DMF
12 in multiple sclerosis, one that skilled artisans could
13 successfully arrive at through routine optimization in light of
14 the prior art.

15 Now, I'd like to walk through some of the key prior
16 art that the Court will hear about during the course of the
17 trial, but first let me say a few words about multiple
18 sclerosis.

19 So it's an autoimmune disease of the central nervous
20 system, and in MS a patient's immune system attacks the
21 patient's own nervous system cells. Specifically, it attacks a
22 substance called myelin that usually forms a protective sheath
23 around nerve fibers resulting in damage that's called
24 demyelination. Without that protective layer of myelin, signal
25 transduction and information flow is impaired and the nerve

1 cells become damaged.

2 And the areas of demyelination is called lesions or
3 plaques, and the Court will hear throughout the course of the
4 trial a lot of talk about these lesions. And this damage can
5 manifest in a wide array of physical symptoms in MS patients,
6 such as vision changes, numbness, muscle weakness, loss of
7 bladder and bowel control, fatigue, and depression.

8 Now, the most common type of MS is called
9 "relapsing-remitting multiple sclerosis." And the parties will
10 refer to that as RRMS.

11 Patients with RRMS experience defined relapses or
12 exacerbations followed by partial to full recovery of
13 neurological deficits over weeks and months. And
14 Dr. Greenberg, our expert, will go into more detail. But, with
15 that brief background on the disease, I'd like to turn now to
16 the prior art.

17 So, long before the priority date of the '514 patent,
18 DMF was successfully used to treat psoriasis. And, like MS,
19 psoriasis is an autoimmune disease; and, as I've said,
20 autoimmune diseases are ones in which, rather than attacking a
21 foreign agent like a virus, the immune system becomes confused
22 and mistakenly attacks the self and it attacks part of a
23 person's own body. And in the case of psoriasis, the immune
24 system mistakenly attacks the skin. It attacks skin cells.
25 And in the case of MS, the immune system mistakenly attacks

1 central nervous system cells.

2 Well, more than a decade before the priority date,
3 skilled artisans had successfully used DMF to treat psoriasis
4 using a 240-milligram dose of DMF given twice a day. So that's
5 a 480-milligram total daily dose.

6 This use of DMF was reported in the Nieboer paper
7 published in 1990. A company called Fumapharm, that Biogen
8 would later go on to acquire, went on and marketed a product
9 called Fumaderm in Europe for the treatment of psoriasis. And
10 Fumaderm is a mixture of four fumaric acid salts, but it was
11 well known in the prior art that, of the four, DMF was the
12 active component.

13 In fact, Nieboer, 1990, reported just that. One aim
14 of the Nieboer study was to test 480 milligrams a day of DMF to
15 treat patients with psoriasis. Another aim of that study was
16 to determine whether it made any difference if the
17 480 milligrams of DMF was delivered alone as a monotherapy or
18 in combination with the other fumaric acid salts in Fumaderm.

19 And in that study Nieboer concluded that the Fumaderm
20 mixture had no significantly better effect than monotherapy
21 with DMF alone. And that's the second highlighted portion we
22 see here on this slide.

23 And as we go through the prior art, Your Honor, the
24 Court will note that, whenever milligram doses of Fumaderm are
25 being reported in the clinical trials, the prior art reports

1 the dose of DMF in Fumaderm, not the dose of the other
2 components. And that's another indication that skilled
3 artisans clearly recognized that DMF was the relevant active
4 component of Fumaderm.

5 Two years later, in 1992, the Kolbach paper, which we
6 see here, likewise described a successful use of a
7 480 milligram dose of DMF to treat psoriasis. And it also
8 reported this: It reported that no significant differences
9 could be found between DMF monotherapy on the one hand and
10 therapy with a Fumaderm mixture of fumaric acid salts on the
11 other when equivalent doses of DMF were taken. Again, it was
12 the DMF that was doing the work, and 480 milligrams of DMF was
13 effective for treating psoriasis.

14 Now, why are we talking about psoriasis? Well,
15 neurologists who treat MS patients took note of the successful
16 use of DMF to treat psoriasis, and that's because psoriasis and
17 MS share similar immunological pathways. And the prior art
18 expressly makes that link between DMF's successful use to treat
19 psoriasis and the motivation to use DMF to treat MS. That
20 motivation, as we'll see in a moment, is made explicit in
21 multiple prior art references.

22 Before I get to that, let me say a word about the
23 immunology that's discussed in these references.

24 As Mylan's expert, Dr. Greenberg, will explain,
25 before the priority date, a prevailing theory of immune

1 dysfunction in both psoriasis and MS was that there's an
2 imbalance of what are called T helper cells in the immune
3 system. And, very broadly speaking, Th1 cells are
4 proinflammatory cells, and Th2 cells are anti-inflammatory
5 cells.

6 In an autoimmune diseases, the Th1 cells predominate
7 and inflammation gets out of control, causing damage to the
8 affected organ. And we see that here in a little animation
9 we've made.

10 And, as I mentioned earlier, in psoriasis the
11 affected organ is the skin; in multiple sclerosis the affected
12 organ is the central nervous system.

13 Now, promoting a shift in the immune response from
14 proinflammatory Th1 cells to anti-inflammatory Th2 cells was
15 believed to be beneficial in the treatment of both psoriasis
16 and MS. Again, we see that just with a little animation here.
17 And it was thought that DMF could achieve that in both
18 diseases. And Dr. Greenberg will explain how that works.

19 Now, we see this motivation in the prior art here in
20 a number of publications from Dr. Schimrigk and others before
21 the priority date. They're looking to the successful use of
22 DMF to treat psoriasis as express motivation to explore the use
23 of DMF to treat MS because of the similarities in the two
24 diseases' immunological pathways. And these are all
25 observations in publications in the 2004 to 2005 time frame

1 before the priority date of the '514 patent.

2 And, Your Honor, it was not just Dr. Schimrigk and
3 colleagues who drew a connection between the use of DMF to
4 treat psoriasis and its use to treat MS. Dr. Kappos, a very
5 well-respected MS specialist who Biogen hired to lead its
6 Phase 2 clinical trial of DMF to treat MS, also recognized the
7 link between DMF's use in psoriasis and its use in MS. And he
8 himself drew that link in the prior art. And what we see here
9 is what we refer to as the Kappos 2005 poster.

10 In June 2005 Dr. Kappos informed skilled artisans at
11 the 15th Meeting of the European Neurological Society that
12 fumaric acid esters had been used in Germany for the treatment
13 of psoriasis. The efficacy of fumaric acid esters in psoriasis
14 is thought to be mediated in part by their immunomodulatory
15 activity, suggesting that these agents may also be effective in
16 MS. And, notably, Biogen's Dr. O'Neill, one of the '514
17 patent's named inventors, was a coauthor of this poster.

18 So Biogen's criticism that you may hear from time to
19 time during the course of this trial, that skilled artisans
20 would not look to psoriasis literature on DMF for motivation
21 relating to the treatment of MS, is contrary to the prior art
22 that taught just that.

23 I just mentioned Dr. Schimrigk. I want to talk about
24 his prior art study because it's an important one.

25 In 2004 Dr. Schimrigk ran a pilot clinical trial in

1 which he treated MS patients with DMF, dosed as Fumaderm, and
2 measured its impact using MRI.

3 And here on this slide we see the Schimrigk study
4 design.

5 So ten patients with RRMS were administered DMF,
6 dosed as Fumaderm. There was a six-week baseline period with
7 no treatment at all, followed by an 18-week period in which
8 patients ultimately received 720 milligrams of DMF, again dosed
9 as Fumaderm.

10 But, as we can see here in the study design,
11 720 milligrams was actually only given for a portion of that
12 18-week period because the dose was slowly titrated up to
13 720 milligrams to minimize gastrointestinal side effects. And
14 you see the kind of ramp there. That's the titration period.

15 And then, next, there was a four-week washout period
16 in which the patients received no medication at all. And
17 following that washout period, patients were titrated up to a
18 360-milligram dose daily of DMF, which was given for more than
19 ten months.

20 Here we see in an abstract, published in the journal
21 "Multiple Sclerosis" in conjunction with a major MS meeting in
22 October of 2004, Dr. Schimrigk's team reported their results.

23 According to the authors, significant results were
24 seen starting after the 12th week of treatment with DMF.

25 Overall, the DMF therapy significantly reduced the number and

1 volume of gadolinium-enhancing lesions over 70 weeks of
2 treatment. Gadolinium-enhancing lesions refer to what is seen
3 on MRI when a clinician injects a contrast agent called
4 gadolinium into a patient's veins. And, if there's active
5 inflammation going on, the contrast will highlight that area on
6 a brain scan.

7 And it represents active inflammatory disease, and
8 it's an important measure of MS disease activity.

9 So the Schimrigk prior art study suggested to skilled
10 artisans that a dose range of 360 to 720 milligrams per day of
11 DMF was a promising new treatment for relapsing-remitting
12 multiple sclerosis.

13 Now, the Court will hear Biogen criticize the
14 Schimrigk study because it was small. It involved ten
15 patients, and several didn't complete the entire study for
16 various reasons. But before this litigation and before the
17 priority date, Biogen did rely on the results of the Schimrigk
18 study.

19 In prior art publications, Dr. Kappos and Dr. O'Neill
20 described the Schimrigk study as one of the bases for Biogen's
21 decision to conduct its own Phase 2 trial of DMF in MS.

22 This is another excerpt from the Kappos 2005 poster
23 that I mentioned earlier, in which Dr. Kappos and Dr. O'Neill
24 recognized a link between the use of DMF in psoriasis and its
25 use in MS. And as we can see here on this slide, in that same

1 poster describing Biogen's planned Phase 2 study of DMF in MS,
2 they also referenced Dr. Schimrigk's successful use of DMF
3 dosed as Fumaderm to treat MS.

4 Now, the Kappos 2005 poster is also important because
5 it describes the design of Biogen's Phase 2 clinical trial of
6 DMF in MS. And in the poster, as we can see here, skilled
7 artisans learned that Biogen gave DMF the name BG-12. And so
8 the Court will hear, through the course of the trial, the
9 parties refer to BG-12. That's Biogen's DMF product.

10 And they also learned, as we see on this slide, that
11 in the Phase 2 trial approximately 250 patients will be
12 randomized to receive either placebo 120 milligrams per day,
13 360 milligrams per day, and 720 or -- or 720 milligrams per day
14 of DMF.

15 And they learn that, like the Schimrigk study, the
16 study's primary end point will be an MRI end point, the total
17 number of new gadolinium-enhancing lesions at weeks 12, 16, 20,
18 and 24 of the study. And Dr. Kappos, as I've said, is the
19 chair of the Phase 2 study steering committee.

20 Now, Your Honor, we flash forward here to January of
21 2006. And in January of 2006, we get the first announcement of
22 Biogen's Phase 2 trial results. In January 2006 Biogen issued
23 a press release announcing that its Phase 2 trial using DMF to
24 treat patients with relapsing-remitting MS met its primary end
25 point and was successful.

1 So I want to recap what skilled artisans knew as of
2 January 2006.

3 First, DMF is the relative active component in
4 Fumaderm, which has been successfully used to treat psoriasis.
5 Second, DMF monotherapy at a dose of 480 milligrams per day is
6 successful in treating psoriasis in autoimmune disease with
7 an -- important immunological similarities to MS.

8 Third, DMF in a range of 360 milligrams per day to
9 720 milligrams per day successfully treated MS in
10 Dr. Schimrigk's 2004 pilot study.

11 And, fourth, Biogen's Phase 2 trial of DMF
12 monotherapy in approximately 250 patients met its primary
13 efficacy end point, leading to a statistically significant
14 reduction in the total number of gadolinium-enhancing brain
15 lesions as measured by MRI with six months of treatment versus
16 placebo.

17 We don't know from the press release which dose or
18 doses worked, but we know there were only three doses tested.
19 And just like Dr. Schimrigk's study, Biogen tested doses of 360
20 and 720 milligrams per day.

21 And one other thing is notable, Your Honor. No one
22 anywhere in the art proposed testing DMF doses higher than
23 720 milligrams per day in MS or psoriasis.

24 Now, Your Honor, because questions have been raised
25 in this case about the prior art status of certain

1 publications, I want to briefly discuss at this point the
2 difference between Section 102(a) prior art and Section 102(b)
3 prior art. All the prior art that I discussed up to this point
4 is section 102(b) prior art, and that's important because it
5 means Biogen can't get rid of it.

6 Under pre-AIA Section 102(b), we see that here, "A
7 person shall be entitled to a patent unless the invention was
8 patented or described in a printed publication in this or a
9 foreign country or in public use or on sale in this country
10 more than one year prior to the date of the application for
11 patent in the United States."

12 So a reference that is prior art under Section 102(b)
13 remains a prior art reference regardless of whose work it is or
14 whether the inventor claims to have conceived the invention at
15 an earlier date and diligently reduced it to practice.

16 All of the references, as I say, that I've discussed
17 so far are Section 102(b) prior art because they predate the
18 priority application in this case by -- which was filed on
19 February 8, 2007, by more than one year.

20 So that means Biogen can't remove these references as
21 prior art by arguing wrongly, we contend, that the Kappos
22 Phase 2 trial was solely the work of Dr. O'Neill or that he
23 conceived the invention earlier than the application filing
24 date and diligently reduced it to practice.

25 So as of January 2006, prior art teaches that skilled

1 artisans were motivated to use DMF to treat MS and reasonably
2 expected it would be effective for that purpose. And the prior
3 art directed skilled artisans to a dose range in which DMF has
4 shown efficacy in MS running from 360 milligrams to
5 720 milligrams per day.

6 Now, Your Honor, we think this is more than
7 sufficient to make out a case of prima facie obviousness. And
8 I won't belabor the law, Your Honor, but here are a couple of
9 cases we think are important discussing the relevant legal
10 principle.

11 This is the federal circuit noting that "For decades,
12 it has recognized that, where the general conditions of a claim
13 are disclosed in the prior art, it is not inventive to discover
14 the optimum or workable ranges by routine experimentation. A
15 more specific application of that general principle is that a
16 prima facie case of obviousness typically exists when the
17 ranges of a claimed composition overlap the ranges disclosed in
18 the prior art." That's the DuPont case from 2018.

19 And then just this year, in January, the federal
20 circuit issued another opinion applying the same principles,
21 noting that "The normal desire of scientists or artisans to
22 improve upon what is already generally known provides the
23 motivation to determine where in a disclosed set of ranges is
24 the optimum combination."

25 Now, Your Honor, prima facie obviousness also squares

1 with the patent office's finding in a previous IPR -- not
2 Mylan's pending IPR, but a previous IPR actually filed by a
3 hedge fund -- that the '514 patent claims are prima facie
4 obvious.

5 Now, the patent was ultimately upheld in that
6 proceeding because the petitioner there failed to put in any
7 evidence -- any evidence -- rebutting Biogen's secondary
8 considerations arguments. And that's certainly not going to be
9 the case here, Your Honor.

10 We will rebut that evidence, and I'll address
11 secondary considerations a bit later. But the point here is
12 that the PTAB has concluded once already that the '514 patent
13 claims are prima facie obvious.

14 Now, I want to make just a couple of additional
15 points on motivation which drive the obviousness conclusion
16 home.

17 First, skilled artisans are motivated to find the
18 minimum effective dose of a drug. And finding the minimum
19 effective dose was a particular concern with DMF because it was
20 well known to have side effects, including unpleasant
21 gastrointestinal side effects.

22 Second, DMF was traditionally dosed three times per
23 day in 120 milligram doses. For example, the 720 milligram
24 dose would be administered as two 120-milligram doses given at
25 three points during the day. Skilled artisans knew that the

1 requirement for such frequent dosing negatively impacts patient
2 compliance with their treatment regimens.

3 And that's especially true in MS, where patients can
4 go long periods of time between relapses, where they don't
5 experience any disease symptoms. And simply put, Your Honor,
6 patients prefer less-frequent dosing. Skilled artisans knew
7 that, and it was a motivation. A lower dose of DMF of
8 480 milligrams per day would allow for twice-a-day dosing,
9 leading to improved patient convenience and compliance.

10 Now, Your Honor, I'd like to turn to two additional
11 publications that are prior art under Section 102(a). And this
12 is Section 102(a) art because it was published within --
13 within -- one year or less of the '514 application filing date,
14 and that's, again, February 8, 2007. And all of this art that
15 I'm about to discuss relates to the Kappos Phase 2 trial of DMF
16 in MS.

17 Now, all of this, we say, is properly considered
18 prior art, and I'll explain why in a bit. But none of the
19 Section 102(a) art that I'm about to discuss is necessary to
20 make out a case of obviousness. The prior art under 102(b)
21 that I've already discussed is more than sufficient for that
22 purpose.

23 So having said that, let me start with the -- with an
24 abstract published in May of 2006 in the Journal of Neurology
25 in conjunction with a meeting of the European Neurological

1 Society, one of the largest associations of neurologists in the
2 world.

3 The abstract lists 14 different authors. And the
4 first listed author is Dr. Kappos. Dr. O'Neill is also an
5 author. But it's Section 102(a) prior art on its face because
6 it lists numerous authors besides Dr. O'Neill. And like the
7 January 2006 press release, the abstract discusses the
8 successful Phase 2 trial of DMF in MS, but it adds more detail.

9 The abstract confirms that the 720-milligram daily
10 dose of DMF was effective. It also reports that DMF
11 significantly reduces brain lesion activity in a dose-dependent
12 manner as measured by MRI in patients with RRMS over 24 weeks
13 of treatment. And that's more motivation, Your Honor, for
14 skilled artisans to explore, through a routine optimization,
15 the minimum effective dose.

16 Now, the second piece of 102(a) prior art is the
17 Kappos 2006 slide presentation. And these are slides that
18 Dr. Kappos -- not Dr. O'Neill, but Dr. Kappos -- presented at
19 the same meeting of European neurologists on May 30th, 2006.

20 And like the abstract, the slide presentation lists
21 14 different authors. And so it's Section 102(a) prior art on
22 its face. And the Kappos slides provide even more detail about
23 the Phase 2 trial and its outcome.

24 So, first, in the presentation, Dr. Kappos notes
25 that -- and we see that on the slide here -- "Fumaric acid

1 therapy has shown efficacy in immune disorders, including
2 psoriasis." He cites the Nieboer 1990 study in which
3 480 milligrams of DMF monotherapy was successfully used to
4 treat psoriasis.

5 He then cites and shows the results of
6 Dr. Schimrigk's study which used 360- and 720-milligram daily
7 doses of DMF, dosed as Fumaderm, to treat MS.

8 So when the Court hears Biogen criticizing the prior
9 art psoriasis studies and criticizing Dr. Schimrigk's MS
10 studies during this trial in the context of litigation, we ask
11 that it remember what Dr. Kappos said about these same studies
12 in 2006 when presenting Biogen's Phase 2 trial results to one
13 of the largest conferences of neurologists in the world.

14 So, Your Honor, this slide reports the Phase 2 study
15 finding on the MRI-based primary end point. As I've said,
16 patients were randomized to one of four treatment groups, or
17 treatment arms, in the study. There was a placebo group and
18 groups receiving 120 milligrams QD -- so that's daily -- 120
19 milligrams TID -- so that's three times a day, so
20 360 milligrams per day -- and 240 milligrams TID, again, three
21 times a day, so that's 720 milligrams per day.

22 And the result for the group of patients randomized
23 to the 720-milligrams-per-day treatment group, which we see on
24 the far right in the slide, reached statistical significance on
25 the primary end point. But according to this slide, the other

1 two DMF groups, 120 milligrams and 360 milligrams, did not.

2 But there's another slide in the Kappos presentation
3 that is critical for understanding these results. In the slide
4 that we see here on the left, which is from Dr. Kappos's
5 presentation, we see the baseline patient characteristics of
6 the patients in the four arms of the study.

7 And the Court will hear from Dr. Greenberg that one
8 thing on this slide jumps out immediately to a skilled artisan.
9 There was a failure of randomization.

10 At baseline, before they entered the study, patients
11 in the 360-milligram-per-day group had more than three times
12 the number of gadolinium-enhancing lesions on average than the
13 patients in the placebo group.

14 And we see that in Dr. Kappos's slide in the bottom
15 row. That's what we've got boxed there in the yellow box. And
16 we've made a bar graph to illustrate the difference, which is
17 there on the right.

18 So the patients in the placebo group -- in the
19 placebo group -- had a mean number of .8 gad-enhancing lesions
20 at baseline when they entered the study. The patients in the
21 120-milligram group and the 720-milligram groups had a mean
22 number of 1.2 gad-enhancing lesions at baseline.

23 But the patients in the 360-milligram-per-day group
24 had a mean of 2.5 gad-enhancing lesions at baseline. And the
25 Court will hear that that means that, on average, their MS was

1 more active. They had a higher level of disease activity
2 coming into the study than did the patients in the other
3 groups.

4 And Dr. Greenberg will explain that current MRI
5 disease activity is predictive of future disease activity. And
6 this imbalance, Your Honor, is particularly striking because it
7 directly impacts the study's primary end point, which was a
8 gad-enhancing lesion MRI primary end point.

9 Now, the Court will also hear from Dr. Greenberg that
10 skilled artisans, when viewing these results, could easily
11 account for the failure of randomization by making either one
12 of two simple calculations. And one of those calculations is
13 shown here. And Dr. Greenberg will go through it.

14 And when the calculations are made, skilled artisans
15 would fully expect that the 360-milligram-per-day dose of DMF
16 also showed efficacy similar to that of the 720-milligram dose
17 in treating MS in the Phase 2 trial. So the Kappos Phase 2
18 trial is further evidence of the '514 patent's obviousness.

19 Now, at this point, I want to very briefly address
20 Biogen's argument that the Section 102(a) Kappos Phase 2 study
21 references they published within a year of the priority date
22 are not prior art because they are solely the work of
23 Dr. O'Neill.

24 As I mentioned earlier, these references each list
25 many other authors than Dr. O'Neill, most prominently,

1 Dr. Kappos is the first listed author on these publications.
2 And it was Dr. Kappos who made the public presentation at the
3 European Neurological Society meeting in Switzerland. And
4 because of this, Biogen -- Biogen has the burden of showing
5 that the disclosures in these references are nevertheless
6 Dr. O'Neill's original work and his alone.

7 Biogen cannot make that showing.

8 First, as I'll discuss a bit later, the evidence will
9 show that Dr. O'Neill did not decide which doses would be
10 included in the Phase 2 trial. Both of his preferred options
11 were rejected by Biogen's clinical trial review board.
12 Biogen's commercial group, not Dr. O'Neill, drove the decision
13 about which doses to include in the Phase 2 study.

14 Second, contemporaneous publications themselves
15 describe the authors' respective roles in the Phase 2 trial
16 and, in particular, the very significant role played by
17 Dr. Kappos, who had the ultimate decision-making authority on
18 whether to submit that study for publication or not.

19 And I want to emphasize, Your Honor, the question
20 here is not -- the question here is not whether Dr. O'Neill
21 conceived of the 480-milligram dose. There isn't even a
22 480-milligram dose in the Phase 2 study.

23 The question is whether this entire Phase 2 trial is
24 solely Dr. O'Neill's original work rather than the work of
25 Dr. O'Neill and others, like Dr. Kappos. And Biogen, we think,

1 will be unable to carry its burden to show that the Phase 2
2 study was solely Dr. O'Neill's work.

3 So, Your Honor, having gone through some of the
4 significant prior art, I'd now like to talk about secondary
5 considerations of nonobviousness. And this is just a summary
6 on this slide of some of the points we'll make when it comes
7 time for us to rebut Biogen's purported evidence of secondary
8 considerations.

9 Now, to attempt to overcome Mylan's strong prima
10 facie showing of obviousness, Biogen argues unexpected results.
11 And, here, the Kappos Phase 2 trial is important for another
12 reason.

13 Biogen's unexpected results argument hinges in large
14 part on the erroneous belief that the 360-milligram-per-day
15 dose of DMF showed no efficacy in the Kappos Phase 2 trial.
16 And based on that premise, Biogen has argued that skilled
17 artisans would not have expected a 480-milligram-per-day dose
18 to show efficacy at all or at least not efficacy comparable to
19 the 720-milligram-day dose in the larger Phase 3 studies that
20 followed.

21 But as we just went over, that's a false premise. If
22 you account for the much higher mean baseline lesion activity
23 of the patients in the 360-milligram-per-day dosing group in
24 the Phase 2 trial, as skilled artisans would indeed have done,
25 then you see that the 360-milligram-per-day dose and the

1 720-milligram-per-day dose have comparable efficacy.

2 And of course you also have Dr. Schimrigk's study in
3 the prior art and his study results using 360 milligrams and
4 720 milligrams per day of DMF dosed as Fumaderm in MS. And, in
5 light of that, the fact that the 480-milligram dose showed
6 efficacy comparable to the 720-milligram-a-day dose in the
7 later Phase 3 trials would be expected.

8 Now, importantly, Your Honor, the baseline lesion
9 imbalance and its impact was recognized by skilled artisans.
10 Indeed, it was recognized by Dr. Kappos himself. In a paper
11 published in 2008 describing the results of the Phase 2 trial.

12 Specifically, Dr. Kappos first notes that the
13 720-milligram-per-day dose had met the primary end point. Then
14 he goes on. Patients in the BG-12
15 120-milligrams-three-times-daily groups -- so that's the
16 360-milligram-a-day group -- had a higher baseline
17 gad-enhancing lesion count compared with other treatment
18 groups, which explained the absence of a more pronounced
19 reduction in new gad-enhancing lesions in this group.

20 Now, Your Honor, this paper was published in 2008.
21 It's after the priority date. And so, because of that, we
22 don't rely on it to show prima facie obviousness. But it does
23 show how skilled artisans would have interpreted the data
24 presented in the Kappos slides.

25 They would recognize that significant baseline lesion

1 imbalance in the 360-milligram-per-day dosing group, and they
2 would have interpreted it in the same way that Mylan's expert,
3 Dr. Greenberg, does. And it was published -- this -- Kappos
4 2008 article was published long before the results of either of
5 Biogen's Phase 3 trials of 480 milligrams per day was
6 available. So those results weren't available when Kappos 2008
7 was published.

8 Dr. Kappos wasn't the only one to publish on the
9 baseline lesion imbalance. This is a book chapter authored by
10 Drs. Ralf Gold and Robert Fox. Dr. Gold is one of the
11 clinicians involved in the Kappos Phase 2 study. And he's a
12 coauthor of the 2006 Kappos abstract and of the 2006 Kappos
13 slide presentation. And he was also the lead investigator on
14 Biogen's defined Phase 3 clinical trial.

15 Dr. Fox was the lead investigator of Biogen's CONFIRM
16 Phase 3 clinical trial. And in this chapter, Drs. Fox and Gold
17 note that the 360-milligram-per-day group in the Phase 2 trial
18 had a 76-percent higher mean number of gad-enhancing lesions at
19 baseline, which may have obscured a treatment effect.

20 If the primary outcome is redisplayed as percent
21 reduction from each group's baseline-enhancing lesion activity,
22 a dose response becomes more apparent. And you see they cite
23 Figure 31.4 for that proposition.

24 And here on this slide we see that figure. So on the
25 left, we see the baseline lesion imbalance. Those are the

1 black bars. And the results without adjusting for the baseline
2 lesion imbalance, those are the gray bars in the box on the
3 right.

4 And then, on the right, Drs. Fox and Gold show the
5 results when you correct for the baseline lesion imbalance by
6 assessing the percent reduction in lesions compared with each
7 group's baseline. And you see, when you do that, the dose
8 response in the 360-milligram-per-day group.

9 Now, this paper too was published after the priority
10 date. So we don't rely on it to show obviousness. But it does
11 show how a skilled artisan would have interpreted the baseline
12 lesion data presented in the Kappos 2006 slides.

13 Now, Biogen has another unexpected results argument.
14 They contend that the magnitude of efficacy that the
15 480-per-milligram-per-day dose displayed in Phase 3 trials on a
16 clinical outcome measures -- not MRI now, but a clinical
17 outcome measure -- annualized relapse rate was unexpected in
18 view of the Phase 2 trial results. But the evidence will show
19 that Biogen is wrong about that too.

20 According to Biogen, the Phase 2 results would have
21 led skilled artisans to believe that DMF would have efficacy in
22 terms of reducing relapses comparable to other
23 disease-modifying therapies that were on the market at the
24 time, but the Phase 3 trial showed it actually performed better
25 than those therapies in reducing relapses.

1 Well, there are several problems with that theory.

2 The first is that the Phase 2 study was not designed
3 to draw reliable conclusions about annualized relapse rate.
4 The evidence will clearly show that the Phase 2 study was not
5 adequately powered to assess that end point.

6 And we see that in the Kappos slides itself here in
7 the yellow box, "Study was not powered for this end point."
8 That's where they're talking about annualized relapse rate.

9 In fact, according to the Phase 2 study, the lowest
10 dose tested, 120 milligrams per day, showed the greatest
11 percentage reduction in annualized relapse rate compared to
12 placebo. But Biogen ignores that inconvenient result in
13 claiming that the annualized relapse rate findings in the
14 Kappos Phase 2 study are reliable.

15 Now, second, the Kappos Phase 2 study was a six-month
16 study. By contrast, the Phase 3 studies on which Biogen relies
17 for their comparison each lasted for two full years and
18 involved far more patients than the Kappos Phase 2 study.

19 And in those studies, annualized relapse rate, or the
20 proportion of patients who had relapse by two years, was the
21 primary end point. They were statistically powered to assess
22 that end point compared to placebo.

23 Skilled artisans do not draw scientifically reliable
24 conclusions about the expected magnitude of efficacy of a drug
25 by comparing a six-month Phase 2 study that is not powered to

1 assess annualized relapse rate to much longer Phase 3 studies
2 which are designed to do just that.

3 And in any event, Your Honor, any difference between
4 the Phase 2 and 3 trials in terms of annualized relapse rate
5 represents a difference in degree, not a difference in kind as
6 the law requires.

7 In terms of secondary considerations, Biogen also
8 argues a long-felt but unmet need for a safe and effective oral
9 MS treatment. That argument is insubstantial. The fact that
10 Biogen's Tecfidera -- that's the brand name for their DMF
11 product -- was the first oral MS treatment to receive FDA
12 approval is not the relevant legal question.

13 The law does not require FDA approval of a drug
14 before it can satisfy a long-felt unmet need. What matters is
15 that the prior art, including the Schimrigk study and the
16 January 2006 Biogen press release, disclosed the effective and
17 safe treatment of MS with oral DMF. And under those
18 circumstances, the law, as we see here in the Novartis case,
19 says you can't show a long-felt but unmet need.

20 Let me address commercial success, another secondary
21 consideration, Your Honor.

22 We also expect Biogen to argue that Tecfidera has
23 been a commercial success and that the market performance
24 supposedly supports nonobviousness. But the evidence will show
25 there are also several flaws with that argument.

1 First, the federal circuit has explained that
2 commercial success carries little weight when the market
3 performance of a product is attributable to monopoly power or
4 other economic coercion or to other factors unrelated to patent
5 validity. And the Court will hear that this type of market
6 power was present here.

7 Namely, Biogen held intellectual property that
8 disincentivized potential competitors from developing the
9 claimed treatment methods. Specifically, as of the priority
10 date, Biogen held patent rights covering Tecfidera. That's the
11 '376 patent that I mentioned at the very outset that was
12 asserted against Mylan in this case but has now expired.

13 And Biogen had applied for the '999 patent in July
14 2002, which ultimately issued with claims that broadly covered
15 DMF formulations for the treatment of MS. And they acted as a
16 strong disincentive to competition.

17 Now, beyond that threshold issue, Biogen fails to
18 consider other facts that negate the required nexus between
19 Tecfidera's market performance and the asserted claims of the
20 '514 patent. Biogen fails to consider aspects of Tecfidera
21 that drove marketplace performance but were known in the prior
22 art already or were covered by Biogen's other patents on
23 Tecfidera. And, therefore, that can't be attributed to the
24 '514 patent.

25 And Biogen minimizes other drivers of Tecfidera

1 sales, such as discounts and allowances and Biogen's extensive
2 marketing and promotion of Tecfidera. So, as a result, the
3 market performance of Tecfidera cannot provide meaningful
4 evidence of nonobviousness and, certainly, evidence sufficient
5 to outweigh Mylan's strong prima facie showing of obviousness.

6 And, Your Honor, the last one I'll just mention very
7 briefly. I don't even know if they're going to assert it in
8 this case. But copying can be a secondary consideration of
9 nonobviousness. But that is not relevant here.

10 The federal circuit has held that, in the
11 Hatch-Waxman context, including with method-of-treatment
12 patents such as those at issue here, copying is not probative
13 of nonobviousness because a showing of bioequivalence is
14 required of generic drugs to receive FDA approval.

15 Your Honor, I want to turn now to Mylan's written
16 description and enablement defenses. And these represent
17 additional independent reasons that the '514 patent claims are
18 invalid. And those defenses are best understood in the context
19 of how the '514 patent came into being.

20 It's an interesting story in and of itself, and it
21 goes a long way to explaining why you can read the '514 patent
22 specification from front to back and find only a single,
23 solitary reference in that entire specification to a
24 480-milligram dose of DMF.

25 The evidence will clearly show that the patent

1 application to which the '514 patent claims priority was never
2 intended to cover a method of treating MS with a
3 therapeutically effective 480-milligram dose of DMF. It was
4 directed to methods of screening for new drugs.

5 And that helps explain why it fails to satisfy the
6 written description and enablement requirements. Indeed, as
7 I'll explain, the evidence will show that, for commercial
8 reasons, Biogen, as opposed to Dr. O'Neill, had little interest
9 in pursuing a 480-milligram dose of DMF to treat MS and had
10 opted instead to pursue a higher dose of 720 milligrams.

11 And, certainly, Your Honor, if the wealth of prior
12 art that we've been over this morning does not render the '514
13 patent claims obvious, then the scant disclosure in this patent
14 specification does not provide legally adequate written
15 description or enablement.

16 So the history here goes all the way back to when
17 Biogen was planning the Phase 2 study of DMF in MS. The
18 evidence will show that Biogen was considering four potential
19 dosing regimens for the Phase 2 trial. And we see them here in
20 a presentation that Dr. O'Neill made to Biogen's clinical trial
21 review board. Parties sometimes call that the CTRB.

22 Biogen's CTRB had the ultimate authority to review
23 and approve proposed clinical trial designs. And Dr. O'Neill,
24 one of the inventors, wanted to include a 480-milligram dose of
25 DMF in the Phase 2 trial. And we see that here in Options 1

1 and 2. Each of those options included a 480-milligram dose.
2 And the evidence will show that Option 1 was Dr. O'Neill's
3 preferred choice.

4 But at the meeting of the CTRB, they rejected
5 Dr. O'Neill's preferred options. We see that in the CTRB
6 meeting minutes here. There were different interests within
7 Biogen, research and commercial, with competing agendas for the
8 Phase 2 trial. And, ultimately, Dr. O'Neill, representing the
9 research group, lost out to Biogen's commercial group.

10 Dr. O'Neill's proposal to include a 480-milligram
11 daily dose in the Phase 2 trial was rejected. He didn't have
12 the authority to select the doses that went into that trial.
13 That authority lay elsewhere in Biogen. And so this is how we
14 end up with the doses that go into the Phase 2 trial of 120,
15 360, and 720, but not 480.

16 Why was Dr. O'Neill's preferred choice rejected?

17 The Court will hear at this same time Biogen was
18 pursuing a DMF product for use in treating psoriasis. And the
19 last thing they wanted was a study showing that a lower dose
20 than 720 milligrams per day of DMF was effective in treating MS
21 because that could undercut the price that they could charge
22 for DMF in psoriasis and in MS. Biogen knew that higher doses
23 meant higher prices.

24 And here are a couple of documents that the Court
25 will see in evidence in the deposition testimony of one of

1 Biogen's employees.

2 This is an email from John Oram, "your man for
3 commercial," as he describes himself, in January 2004, the
4 month before the CTRB meeting. In this email he suggests,
5 among other things, testing higher doses in MS. "Higher dose;
6 higher price."

7 This is an email from September 2005.

8 "The results of the Phase 2 study aren't in yet, but
9 Biogen is starting to think ahead to Phase 3."

10 And this is an email to Dr. O'Neill and others, and
11 you can see everyone still understands the commercial
12 constraint. 720 milligrams is the only viable dose from a
13 commercial perspective. But they recognize -- they
14 recognize -- that they may have a problem on their hands if the
15 Phase 2 trial results show efficacy at 360 milligrams. If that
16 happens, regulatory agencies might make them go with the lower
17 dose.

18 So the upshot, Your Honor, is that Biogen's DMF
19 dosing strategy is being driven by commercial concerns. And we
20 think the evidence will make that clear.

21 Now, let me talk about the Phase 3 trials of DMF in
22 MS.

23 You'll hear from Biogen that they always planned --
24 they always planned to include a 480-milligram dose of DMF in
25 their Phase 3 trials. We think the evidence will show

1 otherwise. They excluded that dose from the Phase 2 trial for
2 economic reasons. They were aiming for a 720-milligram dose in
3 MS because it would mean more profits.

4 Now, they did make plans to include a 480-milligram
5 dose in the Phase 3 trials but only as a contingency. You'll
6 see that referred to as a contingency plan in the event they
7 came to the conclusion that the FDA would require it.

8 In preparation for Biogen's end-of-Phase-2 meeting
9 with FDA -- and the Court will hear the parties refer to that
10 as the EOP2 meeting -- to discuss Phase 3 studies, Biogen
11 submitted Phase 3 proposals that did not include a
12 480-milligram daily dose. And we see they asked the FDA here
13 on this slide "Is our dose selection appropriate?"

14 But in response FDA told Biogen that it should
15 consider testing intermediate doses in the Phase 3 study, e.g.,
16 240 milligrams BID. So that's 480 milligrams a day or
17 120 milligrams three times a day. FDA noted that such dosing
18 regimens could increase patient compliance and minimize side
19 effects.

20 Nevertheless, at the bottom of the page, we see that
21 in the EOP2 meeting Biogen continued to insist that
22 720 milligrams a day was the best choice for the Phase 3
23 studies.

24 Now, ultimately, Your Honor, Biogen relented. After
25 its meeting with FDA, it agreed to add a 480-milligram arm to

1 the Phase 3 studies.

2 Now, when the Phase 3 study results come in in 2011
3 and they showed a positive result for the 480-milligram dose,
4 Biogen finds itself in a bit of a bind. They need a patent
5 application to cover that dose, but they need it to have an
6 earlier priority date than 2011. They need an earlier date
7 that will, because it's earlier, avoid a lot of the prior art.

8 So what do they do? They identify a provisional
9 patent application filed back in 2007 that is titled "NRF2
10 Screening Assays and Related Methods and Composition." It's
11 directed to screening tests to be used to identify new
12 molecules or compounds to treat neurological diseases. We see
13 that rationale here.

14 Fumaric acid esters, such as DMF, have been proposed
15 for the treatment of MS. They cite the Schimrigk study for
16 that proposition. Then it goes on:

17 "The finding that DMF activates the NRF2 pathway in
18 conjunction with the neuroprotective effects of DMF further
19 offers a rationale for identification of structurally and/or
20 mechanistically related molecules that would be expected to be
21 therapeutically effective for the treatment of neurological
22 disorders, such as, e.g., MS."

23 The patent is speaking of screening for new drugs
24 that act in a similar fashion to DMF for the treatment of MS
25 and other neurological diseases.

1 This is the PCT application. We see original Claim 1
2 here. It's a method for evaluating neuroprotective properties
3 of a test compound. Again, the patent is directed to methods
4 for identifying new compounds not using DMF to treat MS.

5 Now, we also see here that, as originally filed, the
6 application names a single inventor, a Biogen employee named
7 Matvey Lukashev. You'll hear from Dr. Lukashev in this case.
8 He's not a medical doctor. His job at Biogen was doing drug
9 discovery research and studying DMF's mechanism of action. He
10 did not have direct involvement with clinical trials. And this
11 patent application, as initially filed, had no claims to the
12 use of DMF to treat a disease and no claims to any specific
13 amounts of DMF.

14 But in June 2011 the Phase 3 results are out. And
15 Biogen effectively takes the Lukashev patent application, and
16 they repurpose it. They give it a new title. You see that in
17 the bottom box here. "NRF2 Screening Assays and Related
18 Methods and Compositions" struck out. New title, "Treatment
19 for Multiple Sclerosis."

20 They add new claims. You see that here as well. To
21 a 480-milligram-per-day dose of DMF to treat MS. And in
22 October 2011 they amend the patent to add Dr. O'Neill for the
23 first time as an inventor.

24 Now, they can't add new material to the specification
25 at this point because, if they do that, they lose the 2007

1 priority date. So they can amend the claims; they can add an
2 inventor; but they're stuck with the Lukashev specification.

3 Now, Your Honor, we fully acknowledge -- fully
4 acknowledge -- that a single patent can claim multiple
5 inventions and a specification can disclose multiple
6 inventions. We don't dispute that at all. But what is also
7 indisputable is that each invention claimed must satisfy the
8 written description and enablement requirements. And, because
9 the '514 patent specification was never drafted to cover
10 methods of treatment claims using a specific therapeutically
11 effective DMF dose of 480 milligrams per day to treat MS, it
12 has no written description for those claims.

13 Now, again, the Court, I know, is familiar with the
14 law. So I'll just touch briefly on it.

15 The written description requirement is satisfied only
16 if the inventor conveys with reasonable clarity to those
17 skilled in the art that, as of the filing date sought, he or
18 she was in possession of the invention and demonstrates that by
19 disclosure in the specification of the patent. That's the Nuvo
20 v. Dr. Reddy's case from the federal circuit last year.

21 And, as the Nuvo case makes clear -- and we think
22 it's an important case, Your Honor, and it's one you will see,
23 I think, quite frequently in the posttrial briefing. This is
24 particularly true where an inventor expressly claims
25 therapeutic efficacy for a particular pharmaceutical compound

1 as the inventors do here. You don't necessarily need clinical
2 data or a specific theory explaining efficacy, but here the
3 therapeutic efficacy of the specific 480-milligram dose has to
4 be supported by specific disclosure in the specification, and
5 it's not.

6 One other case, Your Honor, important principle from
7 the federal circuit, "written description requires something
8 more than that which would render a claim obvious." Another
9 important principle to keep in mind.

10 Now, I said we'd hear from Dr. Lukashev in the case.
11 He'll testify by deposition. They are not bringing him to
12 testify live. But he will confirm that the data in the
13 examples in the patent specification do not shed light on
14 whether DMF will be effective in treating MS in humans.

15 Now, I've mentioned before, 480 milligrams appears
16 once in the specification, the entire specification. There are
17 three examples, four figures, 28 columns of disclosure; and
18 480 milligrams appears once. That's in Column 18 and in the
19 paragraph that starts at line 52 and runs through 64.

20 And that paragraph contains multiple broad ranges of
21 DMF doses. It does not mention MS. And it includes doses like
22 100 milligrams and 200 milligrams per day that skilled artisans
23 would assume could not be intended for the treatment of MS
24 because the prior art suggested they would be ineffective.

25 480 milligrams in the '514 patent specification is

1 nothing more -- nothing more -- than one of seven bookends to
2 four broad ranges with no indication whatsoever that it would
3 be therapeutically effective in the treatment of MS.

4 Now, Your Honor, Biogen knew how to file a patent
5 application adequately describing the use of a 480-milligram
6 dose of DMF to treat MS. They did so in May 2011 by filing a
7 provisional patent application after they had the results of
8 the Phase 3 trial.

9 And the specification in that application discloses
10 the design of the Phase 3 trial in detail. It describes the
11 dosing regimens tested. It includes the trial data. And it
12 reports the trial results. It names Katherine Dawson, Gilmore
13 O'Neill, and Alfred Sandrock, another Biogen clinician, as
14 inventors.

15 But Biogen abandoned it, presumably because they
16 wanted an earlier priority date. So they repurposed the
17 Lukashev compound screening application with its inadequate
18 disclosure of a 480-milligram dose.

19 Now, the enablement issues, Your Honor, largely
20 overlap with written description. So I'm not going to go into
21 them in any more detail, but for many of the same reasons the
22 '514 patent claims are not enabled.

23 So, fundamentally, Your Honor, our argument is that
24 Biogen's positions are untenable here. If all the information
25 available to skilled artisans in the prior art related to the

1 use of DMF to treat MS and the known effective dose range that
2 includes 480 milligrams is not enough to render the '514 patent
3 claims obvious, if the therapeutic efficacy of that specific
4 dose was truly surprising and totally unexpected, then there is
5 simply no way that this patent specification's skimpy
6 disclosure demonstrate with reasonable clarity that the
7 inventors were in possession of a therapeutically effective
8 method of treating MS with a 480-milligram gram dose of DMF.

9 I thank the Court for listening to a long opening,
10 and we look forward to presenting the evidence to you.

11 THE COURT: Thank you very much.

12 I'm sure that Biogen's opening will probably be of
13 equal length. I suggest we take a 15-minute recess. I'm also
14 going to see if I can do something about the temperature in
15 this courtroom. I know it's extremely warm. I had no idea it
16 would be like this. We'll see what we can do.

17 So we'll resume at 5 after 11:00, and we'll go
18 straight through and take our noon -- our lunch after you're
19 finished.

20 (Recess taken, 10:58 to 11:08.)

21 THE COURT: Are things getting better tempwise?

22 MR. MONROE: Yes. Thank you, Your Honor.

23 THE COURT: We can all thank the longtime court
24 security officer here who apparently knows how to do it, get
25 things set. I think right now we're on air-conditioning.

1 Okay. Happy to hear from you.

2 MR. MONROE: Thank you. May I approach with the
3 demonstratives?

4 THE COURT: Yes.

5 MR. MONROE: Good morning, Your Honor.

6 As the Court is aware, patents are presumed valid,
7 and Mylan has the burden of establishing invalidity by clear
8 and convincing evidence. This, it cannot do. The issues in
9 this case were not as simple as Mylan presented in its pretrial
10 filings or this morning, and Mylan's depiction of the prior art
11 and the history of events regarding the claimed invention are
12 inaccurate and ignore the significant development efforts led
13 by Dr. O'Neill that ultimately led to the claimed invention
14 and, ultimately, the Biogen Tecfidera product.

15 I would like to focus this morning on certain key
16 issues to help guide the Court in its assessment of the
17 evidence during the course of this trial. Specifically, Biogen
18 will present testimony and documents establishing that Mylan
19 has failed to meet its burden in at least the following ways,
20 which are identified on Slide 2, Your Honor.

21 With respect to nonobviousness, the claimed invention
22 is not prima facie obvious in view of the alleged prior art
23 because, as you heard, Your Honor, there's a dispute about
24 certain items being prior art.

25 With respect to that, the materials that Mylan points

1 to include publications of Biogen's Phase 2 study that
2 represent Dr. O'Neill's own work and thus cannot constitute
3 prior art for purposes of an invalidity challenge to the
4 patent.

5 Moreover, Dr. O'Neill's claimed invention of using
6 480 milligrams per day of DMF to treat MS exhibited an
7 unexpected magnitude of efficacy rendering the claimed method
8 nonobvious on this basis alone. Indeed, unexpected results is
9 a cornerstone of nonobviousness.

10 And, finally, Mylan's baseline imbalance argument is
11 scientifically invalid -- and you'll hear testimony about this,
12 Your Honor -- and it cannot be used to rewrite the conclusions
13 specifically taught in the references that Mylan relies on.

14 With respect to Mylan's challenges based on 35 U.S.C.
15 112, the evidence and document will show -- evidence and
16 documents produced in this trial will show that the '514 patent
17 describes and enables the claimed invention.

18 Now, I'd like to turn briefly to the claims at issue.
19 You saw these earlier, Your Honor. The '514 patent contains
20 several claims, both independent and dependent claims. For
21 today's discussion, I will focus on Independent Claim 15 and
22 Dependent Claim 16. And, as shown on Slide 3, Independent
23 Claim 15 is directed to a method of treating a subject in need
24 of treatment for multiple sclerosis comprising orally
25 administering dimethyl fumarate in an amount of about

1 480 milligrams per day.

2 Now, Your Honor, I have highlighted certain terms of
3 the claim in order to prepare us for the discussion regarding
4 written description because we have -- as we go through the
5 patent to show that the patent provides written description,
6 it's helpful to be able to see how all of the elements are --
7 exist throughout the patent.

8 As for Claim 16, Dependent Claim 16, that is a
9 dependent claim that provides the dimethyl fumarate is
10 administered in two equal doses.

11 Now, these claims read directly on Biogen's Tecfidera
12 product, and I don't believe there is any dispute about that.
13 Tecfidera is Biogen's disease-modifying therapy that has
14 changed the lives of thousands and thousands of patients. This
15 therapy involves taking a specific amount of the compound
16 dimethyl fumarate, namely 480 milligrams per day, in two equal
17 doses of about 240 milligrams.

18 Now, Tecfidera was approved by the FDA on March 27th,
19 2013, and is now the most prescribed oral disease-modifying
20 therapy for MS. This therapy has been so successful that it
21 overtook the market for oral MS treatments when it entered the
22 market and has maintained that position ever since.

23 For example, as shown on Slide 5, Tecfidera became
24 the most prescribed oral therapy for relapsing forms of
25 multiple sclerosis six months after its launch. To be clear,

1 and to assist the Court, because the green line represents
2 Tecfidera sales once it launched, and the other two lines
3 represent the competitive products, Gilenya and Aubagio. And,
4 as you can see, as soon as Tecfidera launched, one of those
5 products dropped significantly in the market; the other product
6 never really made much of an impact into the market.

7 Now, Tecfidera's success has, in turn, attracted the
8 attention of an unusually large number of generics. We were at
9 25 plus. Your Honor, this case only involves one of them,
10 Mylan. And they're all attempting to take the benefit of
11 Biogen's discovery.

12 As you hear the evidence, it is important to keep in
13 mind one of the several reasons Tecfidera has been so
14 successful; namely, MS is a highly complex disease and is
15 difficult to treat. And we heard about some of those issues
16 this morning, and we agree with some of the representations
17 regarding the difficulty of treating MS and how bad it is for
18 patients. And on Slide 6 we've tried to highlight why this is
19 such a difficult disease to treat.

20 The pathology of MS is highly complex and poorly
21 understood even today. We have therapies, disease-modifying
22 therapies, but we still don't really know what is causing it
23 and how to cure it. We can simply treat it.

24 In addition, MS worsens over time, and it's
25 devastating and irreversible. That's particularly important,

1 Your Honor, because, with respect to MS, once you have damage,
2 it doesn't go away. It exists. It stays. The sort of items
3 that opposing counsel is referencing continue to be
4 debilitating impacts on the patient.

5 In addition, MS patients go into various relapse and
6 remissions. And, therefore, you don't always know what
7 condition they're in, and it can be sort of an invisible
8 disease. If you were tested during a remission, you wouldn't
9 know the state of their MS. In addition, disease progression
10 varies considerably among patients. And, as I note, it could
11 be invisible when you're doing testing.

12 For all of these reasons, it's very important that
13 you have a long-term therapy that shows effectiveness over a
14 large number of patients. Tecfidera, the commercial embodiment
15 of Dr. O'Neill's invention claimed in the '514 patent, has
16 satisfied that need.

17 I would now like to turn to Mylan's obviousness
18 allegations, which fail for many reasons. For example, they do
19 not reflect how the skilled artisan would have viewed the prior
20 art in 2007 at the time of the filing of the patent application
21 that led to the '514 patent. Indeed, Mylan has stretched so
22 far to find some basis for its position, but it has taken the
23 extreme step of rewriting the unambiguous teachings of the
24 primary references that it relies upon instead of going with
25 those express teachings.

1 In addition, Mylan's rewriting of history based on --
2 is based entirely on hindsight and, similarly, that hindsight
3 has affected the combinations of references that Mylan has put
4 forth in support of its positions. The law is very clear that
5 type of hindsight approach to obviousness is legally improper.

6 Finally, as Mylan noted, Biogen will present evidence
7 during trial that serves as substantial objective indicia of
8 the nonobviousness of the claimed invention. This includes
9 evidence regarding unexpected results, long-felt need that's
10 been now met, copying, and commercial success.

11 Now, we expect Mylan's invalidity positions to be
12 focused on through hindsight on four general categories of
13 information, and I think that the presentation this morning
14 touched on some of those, but I believe they will present
15 additional evidence during their presentation of their expert.

16 The first, as shown on Slide 8, which I will address
17 in more detail later, includes information regarding Biogen's
18 Phase 2 MS study. And Mylan sometimes refers to this Phase 2
19 study and these Phase 2 materials as the Kappos abstract, the
20 Kappos presentation, the Kappos slides.

21 For ease of consistency and to avoid any confusion
22 about which documents we're talking about during this trial, we
23 will adopt that moniker of saying "Kappos abstract" or "Kappos
24 presentation," but we vigorously disagree and will present
25 evidence that those are his abstracts and presentations.

1 Dr. Kappos is the first listed author, but by
2 convention Dr. O'Neill is the last listed author, which puts
3 him as the lead author on the publication. And we'll present
4 evidence that you will hear, Your Honor, that he actually
5 drafted the materials that are now being characterized as
6 Kappos materials.

7 Because they represent his own work, they could not
8 constitute prior art against his claimed invention under
9 102(a).

10 The second type of art that Mylan points to is the
11 use of Fumaderm, discussed in the article that they referred to
12 as Schimrigk. Fumaderm, however, is a mixture of four active
13 ingredients and, at most, teaches that one might consider using
14 1290 milligrams per day of those four active ingredients to
15 treat MS. There is nothing that would lead the skilled artisan
16 to 360 milligrams per day or 720 milligrams per day of DMF
17 alone. And you'll hear arguments, as you heard arguments
18 already, Your Honor. They're saying Schimrigk showed some sort
19 of dose range of DMF from 360 to 720.

20 Well, no. First, it's showing -- it's all about a
21 mixture of components, not about DMF alone. And you'll hear a
22 lot of evidence about that, Your Honor.

23 Secondly, one skilled in the art would not have had
24 any reasonable expectation of success, which is the standard,
25 that dosing information -- this really is about the dose

1 again -- is that the dosing information for a mixture of four
2 active ingredients could be extrapolated to dosing for a
3 different formulation containing only one of those four active
4 ingredients.

5 The third category of art shown on Slide 8 relates to
6 the use of various fumarates to treat psoriasis. One skilled
7 in the art, as you will hear, Your Honor, would not have had
8 any reasonable expectation of success that dosing protocols for
9 one disease, like psoriasis, would be equally applicable to
10 other diseases, like MS.

11 Finally, the fourth category is an assortment of
12 items that do nothing to address the deficiencies of the first
13 three categories. Accordingly, for today, I am going to focus
14 on the first three categories of information that you will hear
15 evidence during trial on the others.

16 But before I move on, I would like to point out that
17 all of the art that has been identified by Mylan was considered
18 by the patent office during prosecution of the '514 patent.

19 Now, I'd now like to provide a little more detail
20 regarding the category of material regarding Biogen's Phase 2
21 study.

22 As shown on Slide 10, the Biogen's Phase 2 study had
23 four dosing arms. One was an inactive dosing arm, the placebo
24 arm -- which I would like to stress, Your Honor, the importance
25 of having a placebo arm when you're doing a clinical trial.

1 That placebo arm is used as a comparator for the three active
2 dosing arms in Phase 2. And those -- as we heard already, Your
3 Honor, those other dosing arms were 120 milligrams per day,
4 360 milligrams per day, and 720 milligrams per day of DMF.

5 Now, one focus of this study was to use MRI to
6 evaluate the reduction of lesions compared to placebo, and
7 another was to evaluate the reduction of the annualized relapse
8 rate compared to placebo.

9 At the end of the study, it was reported that only
10 one dose, the 720-milligram-per-day, had a statistically
11 significant effect. The 120- and 360-milligram-per-day doses
12 were reported to not have a statistically significant effect
13 compared to placebo. There does not appear to be a dispute
14 that the express teaching of the reports that they're relying
15 upon state that only 720 had a statistically significant
16 effect.

17 And to illustrate this point, I'd like to show on
18 Slide 11 certain excerpts from what they refer to as the Kappos
19 presentation. And these are excerpts showing the results.
20 And, if you look at the excerpt on the left of the slide, Your
21 Honor, that is reporting on the number of new Gd+ lesions,
22 which you've heard about previously, from weeks 12 to 24. And
23 that was a prespecified primary end point. So the design was
24 focused on having this be a primary end point for the study.

25 And, as you heard earlier, Your Honor, the column on

1 the left is the placebo. The column on -- to the next of it,
2 to the right, is 120 milligrams per day. The column on the
3 right after that is the 360 milligrams per day. And the last
4 column on the right is the 720-milligrams-per-day dose. And
5 that's the dose that the authors pointed out, through the
6 bracket that you can see, had a 69 percent reduction in new Gd+
7 lesions.

8 We've also provided additional slides -- excerpts on
9 this slide, Your Honor, showing other end points that were used
10 during the course of this study. Specifically, the middle
11 slide shows the results for new Gd+ lesions from weeks 4 to
12 24 -- so a different period -- and that was a secondary end
13 point. And, again, using the bracket on the right, the authors
14 pointed out that only 720 milligrams per day had a
15 statistically significant effect. And in this case it was
16 44 percent.

17 And then finally the slide on the right identifies
18 the results of another secondary MRI end point, mainly new or
19 newly enlarging T2 lesions. That's another type of lesion that
20 is important to monitor. And here it is reported that again
21 the 720-milligram-per-day dose was the only one that showed a
22 statistically significant effect for that end point.

23 Now, as I noted, these are from the -- what's
24 referred to as the Kappos presentation. And Dr. O'Neill is the
25 lead author on that presentation, and it reflects his work.

1 Now, the summary on Slide 12 that I'd like to direct
2 your attention to, that is an excerpt providing a summary of
3 the results of the Phase 2 study. And, again, this represents
4 in text the results that I just showed to you graphically.

5 And this highlights the focus that the 69 percent
6 reduction in Gd+ lesions, the 48 percent reduction for new or
7 enlarging T2 lesions, and the 32 percent reduction on
8 annualized relapse rate were things that made BG-12, which was
9 the -- otherwise, Tecfidera, associated with a trend toward
10 reduced -- with a unique profile for purposes of the results of
11 the Phase 2 study.

12 I referred to BG-12 there as Tecfidera, but for
13 clarity for the Court, Your Honor, at the time of the Phase 2
14 study, as we discussed, they were testing 120, 360, 720 of DMF
15 alone. And BG-12 was the code name used for DMF alone for
16 experimental purposes.

17 Ultimately, as you've already heard, Your Honor, in
18 the Phase 3 trials, the 480-milligram-per-day dose of DMF alone
19 was also called BG-12. And it's actually the
20 480-milligram-per-day dose that is contained in Tecfidera.

21 Now, notwithstanding the positive results of the
22 720-milligram-per-day testing compared to the other doses,
23 these results were unimpressive compared to existing MS
24 therapies.

25 For example, the Court will be provided with

1 testimony and evidence establishing that the 48 percent
2 reduction of new enlarging T2 lesions, that was the slide that
3 was on the far right of what I just showed you, was lower than
4 approved therapies available at that time.

5 And the 32 percent reduction in relapse rate puts
6 720 milligrams per day of DMF in what the skilled artisan
7 called a low-efficacy category. Accordingly, although these
8 results were promising, the lackluster performance of the
9 720-milligram-per-day dose would have motivated a skilled
10 artisan to pursue doses higher than the 720-milligram-per-day
11 dose to increase efficacy.

12 This is especially so given that the presentation
13 also reported that the 720-milligram-per-day dose was, quote,
14 generally safe and well tolerated. And we've provided on
15 Slide 14, Your Honor, additional excerpts from this same
16 presentation which show that the adverse event information with
17 respect to all dosing arms was very similar and unremarkable
18 and led the authors to conclude, based on the results, that
19 BG-12 was generally safe and well tolerated.

20 And if you look at this slide excerpt that's on the
21 left of Slide 14, we've highlighted with a red box the total
22 number of serious adverse events. And you can see, looking
23 across those columns, that the 720-milligram-per-day dose is
24 very similar -- well, exactly the same as the
25 360-milligram-per-day dose and very similar to even the

1 placebo.

2 Similarly, on the right side of the slide, Your
3 Honor, we have identified information regarding
4 discontinuations of -- during the course of the study based on
5 adverse events. And on there, you will see, Your Honor, that
6 the discontinuation numbers for the 360-milligram-per-day and
7 720-milligram-per-day doses were the same and only slightly
8 higher than that for 120 milligrams per day.

9 Accordingly, one skilled in the art seeing the
10 720 milligrams per day had a lackluster efficacy but also was
11 generally well tolerated, a skilled artisan would have been
12 motivated to go higher and look for a more efficacious dose for
13 treating MS.

14 This is because maximizing efficacy is a top priority
15 for MS therapy, for many of the reasons I discussed earlier.
16 And as I just walked through, we believe that the skilled
17 artisan would have targeted going higher than 720 milligrams
18 per day to achieve a higher efficacy given the seriousness of
19 MS.

20 But as I noted earlier, Your Honor, Mylan cannot rely
21 on the reports of Biogen's Phase 2 study results in the first
22 place because these materials represent Dr. O'Neill's own work.

23 I will not go too far into the case law this morning,
24 Your Honor, but I would like to point out, as shown on
25 Slide 17, that the law is clear that, under 35 U.S.C. 102(a),

1 that an inventor's own work published less than one year before
2 patent filing date is not prior art. And there doesn't seem to
3 be any disagreement on that given what we heard from Mylan this
4 morning.

5 In addition, Dr. O'Neill's own work was published
6 less than one year before the '514 patent's filing date, and
7 therefore it doesn't constitute prior art. Obviously, Mylan
8 has continued to argue that it is prior art and that it is not
9 the work of Dr. O'Neill, but there doesn't seem to be any
10 dispute that it was published within a year of the filing date
11 of the application, and therefore, if it is his work, it can't
12 be used against him for their invalidity case.

13 I'd like to highlight just some of the evidence that
14 you're going to hear during the course of the trial regarding
15 why this is his work. Some of it has already been identified
16 to you by Mylan. In particular, I'd like to show on Slide 18,
17 Your Honor.

18 This is a presentation that Dr. O'Neill provided in
19 February of 2004 in which he laid out various dosing options
20 that he would propose Biogen consider for testing DMF alone for
21 MS. And in this presentation he provided the four options.
22 And it is correct that the first two, using 480 milligrams per
23 day, were his preferred options because he believed from the
24 very beginning that 480 milligrams per day would be a dose that
25 would be effective.

1 Based on his own insight, based on his own evaluation
2 of confidential information -- and you'll hear about this, Your
3 Honor -- he believed that was a very important dose and,
4 therefore, included it in his top two options.

5 But he also included an option that didn't have it
6 because, for completeness, he included Option 3. And it's
7 important to note, when you look at Option 3, that it is the
8 Phase 2 study. It is 120 milligrams, 360, and 720. So that
9 was Dr. O'Neill proposing that in February of 2004.

10 We've heard discussions about what the FDA may have
11 done or what commercial may have thought about these things.
12 The CTRB may have thought about what should be dosed. At the
13 end of the day what matters is Dr. O'Neill proposed the 120,
14 360, and 720 dosing protocol that formed the basis of Phase 2.,
15 and therefore that is his work identifying the protocol to be
16 used in Phase 2.

17 Similarly, Dr. O'Neill was responsible for all
18 aspects of the Phase 2 study. He was responsible from design
19 and execution to analysis and reporting of the results. He
20 designed the dosing protocols. And Biogen selected, as we just
21 discussed, Option 3 to move forward into Phase 2. But then he
22 supervised and directed Biogen's employees and external
23 investigators on execution of Phase 2.

24 In addition, the Phase 2 trial data was unlocked and
25 analyzed by Biogen's statistician under his direction. And

1 what I mean by that, Your Honor, is this was a blinded study.
2 The external investigators conducting the study had no idea
3 whether they had the placebo or they had the 360 or the 720 or
4 the 120. And he oversaw, using Biogen's statisticians, the
5 unlocking and analyzing of the data.

6 And the fact that he was the one analyzing the data
7 and reaching conclusions will be shown through evidence
8 regarding how those conclusions were summarized and then
9 transmitted and provided to Dr. Kappos, which -- Mylan always
10 focuses on Dr. Kappos, but if you look, for example, at
11 Slide 20, Your Honor, this shows a comparison of two abstracts.

12 The one on the right is the one that Dr. Kappos was
13 included on that was published in May of 2006. And this
14 reported on a summary of some of the results of the Phase 2
15 study.

16 And if you look to your left, that is the draft
17 abstract that Dr. O'Neill prepared in January of 2006. And
18 they are essentially the same. Dr. O'Neill prepared the
19 summary of the results and then provided it to Dr. Kappos to
20 see if he had any comments, because he was a chief investigator
21 on the study. And he made insubstantial changes to the
22 abstract before its publication.

23 So the fact that -- if they want to rely on this
24 piece of evidence, not every single aspect of the Phase 2
25 study -- obviously, large clinical trials require a number of

1 people to carry them out. But if you want to focus on who
2 designed the study, who oversaw it being carried out, and then
3 who analyzed the results and summarized them, this shows it was
4 Dr. O'Neill who summarized those results. And this piece of
5 prior art contains his work -- his dosing of 120, 360, 720 --
6 and then his conclusions regarding that study.

7 The same analysis applies to the -- what they called
8 the Kappos presentation that we've been talking about. And
9 this is shown -- an example of this is shown on Slide 21, Your
10 Honor.

11 Here, we have on the right-hand side the summary
12 slide I showed you earlier summarizing some of the key findings
13 from the study. In particular, the 69 percent reduction in Gd+
14 lesions and the 32 percent reduction in the annualized relapse
15 rate.

16 Well, if you look on your left, Your Honor, that is
17 the presentation that Dr. O'Neill prepared in January and
18 February of 2006 for certain confidential presentations that he
19 gave. And he then provided -- and you'll hear testimony. He
20 provided that slide set to Dr. Kappos so Dr. Kappos could give
21 the same presentation at a meeting later in May of 2006. So
22 the evidence will again establish, if Mylan wants to focus on
23 that presentation, that it was actually Dr. O'Neill who
24 prepared that presentation.

25 Now I'd like to switch to a different topic, Your

1 Honor, which is the unexpected results shown by the Phase 3
2 study.

3 Even if the Kappos materials were prior art, Biogen
4 did the opposite of what one skilled in the art would have
5 done. Instead of looking to higher doses to obtain better
6 efficacy than the lackluster 720-milligram-per-day dose, Biogen
7 added the 480-milligram-per-day dose.

8 That is because Dr. O'Neill, as I mentioned, his idea
9 from the very beginning was to use 480. And he always believed
10 that Biogen should ultimately use that in the Phase 3. To be
11 clear, this was a risky move on Biogen's part, given that 720
12 only had lackluster efficacy and he was going downward.

13 But, in addition, large Phase 3 trials, as you heard,
14 they're very large and they're very expensive and take a very
15 long time to complete. And this was an especially risky move
16 on Biogen's part given that the additional dose, as I noted,
17 was lower than 720 and closer to the 360 dose that had been
18 established to not be statistically significant for purposes of
19 MS.

20 But Biogen took this risk based on Dr. O'Neill's
21 insight, and doing so paid off. The Phase 3 results
22 unexpectedly showed that the 480-milligram-per-day dose of DMF
23 was not only efficacious but also had a similar effect to that
24 of the 720-milligram-per-day dose. And the result of that is
25 now the public and the MS community, they reap the rewards of

1 that insight by Dr. O'Neill such that they're now being treated
2 with the 480-milligram-per-day dose.

3 Now, I'd like to show on Slide 24 an excerpt from a
4 report of the Phase 3 results. This shows graphically what was
5 such a surprise to everybody when the results came out. We've
6 added some red underlining and some highlighting just to make
7 it clear, because it's not -- the two lines, the one for twice
8 daily and the one for thrice daily -- in other words, the 480
9 and the 720 -- they're right on top of each other. Nobody
10 expected that. That was a very surprising result.

11 And when I say no one, other internal Biogen people
12 were very surprised that that was the result, and also the
13 outside community was very surprised with that result.

14 As to the public perception, you'll hear from
15 Dr. Duddy, who is one of our experts and is an MS expert. And
16 he will provide you with some background on contemporaneous
17 evidence that he created at the time of the release of the
18 results for the Phase 2 and Phase 3 study. And so these are
19 contemporaneously created documents before this litigation ever
20 occurred.

21 The chart on the left represents Dr. Duddy's views in
22 September of 2009 after the Phase 2 results were published.
23 And you will see that he has placed BG-12, based on the Phase 2
24 results, in the bottom left quadrant as being a low-efficacy,
25 low-risk drug.

1 But then skip forward a few years. After the Phase 3
2 results come out, Dr. Duddy recategorized his view with respect
3 to BG-12. And he put it in the high-efficacy, low-risk
4 quadrant. And it's the only drug in that quadrant. And you'll
5 hear more about why he did that during his testimony, Your
6 Honor.

7 Now, given this evidence and the unambiguous
8 teachings of the Phase 2 study, Mylan has turned to the --
9 rewriting history, as I call it, with respect to those results.

10 Specifically, Dr. Greenberg argues that the skilled
11 artisan would have believed that the 360-milligram-per-day dose
12 of DMF was also efficacious despite the express teachings to
13 the contrary.

14 Dr. Greenberg bases this conjecture on the
15 unsupported assertion that the skilled artisan would have been
16 motivated to recalculate the Phase 2 study results due to an
17 alleged imbalance in the Gd+ lesions for the
18 360-milligram-per-day group. And keep in mind that all was
19 reported at this time were mean values. They weren't
20 individual patient data, which you need in order to do that
21 sort of calculation. And you'll hear more about that, Your
22 Honor.

23 But at the end of the day, his argument fails for
24 multiple reasons.

25 First, all of the baseline characteristics in the

1 Biogen Phase 2 study were well balanced.

2 Second, Dr. Greenberg's hindsight recalculation lacks
3 statistical significance and, therefore, is unreliable.

4 Third, Dr. Greenberg alters Biogen's Phase 2 design
5 by disregarding the placebo arm. Again, the placebo arm is one
6 of the most important elements of the design because you're
7 comparing the effects of your drug to the placebo effect.

8 And, in the same fashion, his redesign ignores the
9 temporary nature of lesions.

10 And if I could direct your attention, Your Honor, to
11 Slide 28, this contains an excerpt again of the Kappos Phase 2
12 results that Mylan characterizes that way. And this shows that
13 the baseline patient characteristics for all four of the items
14 that were monitored -- the age; relapse history; the disability
15 score, known as EDSS; and the number of Gd+ lesions -- were all
16 well balanced.

17 And Dr. Duddy will testify that one skilled in the
18 art looking at this information would find and believe that the
19 range of baseline Gd+ lesions were unremarkable and typical.

20 Mylan has done some math with respect to how you can
21 multiply one by another. You can -- that the .8 placebo is a
22 third of the 120 milligrams three times a day, but that's not
23 what the skilled artisan looks at. The skilled artisan looks
24 at whether this would be a typical variation with respect to
25 baseline lesions. And you'll hear testimony and see evidence

1 that the skilled artisan would view it that way.

2 And I think corroborating that evidence that you're
3 going to hear, Your Honor, is that nobody identified any
4 imbalance in the baseline Gd+ lesions during the Phase 2 study
5 or before the 480-milligram-per-day was tested in the Phase 3
6 studies.

7 Indeed, if we could point -- go to Slide 29, Your
8 Honor, I would like to point out one of Dr. Greenberg's own
9 publications in 2008 in which he was reporting on the Phase 2
10 results. And he did not identify any imbalance in the baseline
11 Gd+ lesions.

12 Instead, he called out in particular the
13 720-milligram-per-day dose as being the effective dose in
14 Biogen's Phase 2 study. And he did not characterize
15 360 milligrams per day as an effective dose. And he didn't
16 identify, when reporting on the study, any imbalance in
17 baseline Gd+ lesions.

18 It's only now that we're in this trial, in this
19 litigation, that we're hearing from Dr. Greenberg that he now
20 believes, in hindsight, that there was some sort of error in
21 the Kappos reporting.

22 And with respect to that, we heard this morning, Your
23 Honor, a few comments about postfiling publications. And
24 Mylan's taken the position that those items that they admit are
25 not prior art somehow confirm that 360 milligrams per day

1 likely achieved efficacy.

2 That argument fails because, first, they're not prior
3 art. They were published after the knowledge of the testing of
4 the 480-milligram-per-day dose and its surprising results.
5 Keep in mind the 2008 article included authors who knew what
6 was being tested in the Phase 3 study and therefore had
7 information that others did not.

8 Second, these references simply hypothesized that
9 small differences in baseline lesions might have had an impact,
10 but this was -- never been proven. This has never been proven.
11 And they didn't reach that conclusion ultimately.

12 I'd now like to turn to the issue of Fumaderm, Your
13 Honor. And I think we need to spend just a little bit of time
14 on that issue.

15 Schimrigk is the main reference that Mylan is relying
16 upon if they are not able to rely upon the 102(a) art. And
17 this was an open-label small study, as they noted, of just ten
18 patients. And three patients dropped out in the first three
19 weeks, and therefore the study design of this small study
20 cannot be used to reach any conclusions regarding efficacy.
21 And in particular there's no placebo control. Again, during
22 this small study, the patients could be in remission when they
23 were undergoing examination.

24 In addition, the Schimrigk abstract notes that
25 Schimrigk used Fumaderm. Fumaderm is a combination of four

1 active ingredients. And it was approved -- it was a product --
2 just to give you some background, Your Honor, Fumaderm was a
3 product approved for psoriasis treatment in Germany.

4 And if you look at the label for Fumaderm -- and I've
5 shown that on Slide 33, Your Honor -- the label shows that all
6 four components are active components. It specifically states
7 that all four are active ingredients for treating psoriasis.
8 Obviously, this says nothing about MS. This is all about
9 treating psoriasis. And they say all four are active
10 ingredients.

11 Therefore, one skilled in the art who was using
12 Fumaderm would believe that all four were active ingredients
13 for psoriasis. And they'd have no reason to believe that you
14 could separate out one of those individual components and that
15 it would, on its own, be efficacious.

16 Now, Mylan has argued that Schimrigk somehow admits
17 that it's the -- 720 is the only active ingredient for purposes
18 of -- the testing in his study. Schimrigk does not say that.
19 Schimrigk does note that 720 had the larger amount of drug in
20 the mixture, but amount does not equal more activity or
21 activity.

22 And it's somewhat misleading, Your Honor, when Mylan
23 will refer to Schimrigk's study and say it used 720 milligrams
24 Fumaderm -- 720 milligrams DMF dosed as Fumaderm. Schimrigk
25 doesn't say it's dosing DMF for purposes of the study; it's

1 using the mixture, and it's trying to see what results that
2 mixture has.

3 And another aspect of Fumaderm that I think is worth
4 spending a small amount of time on, Your Honor, is that the
5 label for Fumaderm for treating psoriasis specifically tells
6 one to go up to a dose -- daily dose of 1290 milligrams per
7 day. And that's what Schimrigk used.

8 So Schimrigk did follow the guidance to use
9 1290 milligrams per day of this four-active-ingredient mixture.
10 So one skilled in the art looking at Schimrigk would have had
11 no reason to believe that they should separate out the DMF as
12 an individual component or that they should use lower amounts
13 of that individual component. And that's really what Mylan's
14 position is. And there is no support in that in the art that
15 they cite.

16 I would now like to address briefly Mylan's third
17 category of art. That's the psoriasis art. Well, as we just
18 talked about, the Fumaderm label and what we know about
19 Fumaderm, it was psoriasis art. But a skilled artisan would
20 not have believed that one could adopt a particular dosing
21 protocol for one disease like MS merely because that same dose
22 was used for another disease like psoriasis, let alone with any
23 reasonable expectation of success.

24 And I think it's important to note the differences --
25 the significant differences between these two drugs. Mylan

1 would suggest that they're just all the same. There's some --
2 one little mechanism underlying both that's the same, and
3 therefore you just know you can treat them the same.

4 The evidence will establish, one, that they're wrong
5 on the -- there's just this one underlying mechanism; and, two,
6 even if they were, that does not inform your decision with
7 respect to dosing.

8 And that's because, when you look at these diseases,
9 they're very different, as shown in Slide 36. Psoriasis
10 manifests primarily on the skin, whereas MS manifests in the
11 central nervous system. Those are very different things. The
12 result of that is the treatment effects, when you're treating
13 psoriasis, can be immediately ascertained. You know whether
14 you're having an effect. MS, you don't. You can only
15 ascertain effectiveness for MS over years of treatment by
16 monitoring things like lesions and symptoms. You can't just
17 immediately know a drug had an impact.

18 Similarly, psoriasis patients can cycle on and off
19 treatment. That goes back to lesions for psoriasis on the skin
20 can be temporary, and therefore you see an effect immediately
21 after use of the drug, whereas MS treatment requires
22 continuous, life-long therapy.

23 And that goes back to the point I made earlier, Your
24 Honor, about how sometimes it's an invisible disease and you
25 can't see what's really happening inside the body. And, on top

1 of that, once the damage occurs, it cannot be undone. So your
2 goal is to make sure you stop it before it happens or at least
3 diminish it from happening.

4 And, as a result, you can individually titrate
5 patients for psoriasis, but you cannot, do not, and should not
6 individually dose titrate MS therapies.

7 Indeed, this is another reason that one cannot
8 extrapolate dosing from one disease to another. Indeed, just
9 by way of example -- you'll hear during trial, Your Honor -- is
10 a drug that may work for one disease may make another disease
11 with a similar underlying mechanism even worse.

12 Lenercept is an example of a Th1 inhibitor, and they
13 referred earlier to a Th1 inhibitor. It actually makes MS
14 worse. And you'll hear more about that during this trial, Your
15 Honor.

16 Now, Mylan points to a couple of psoriasis
17 publications. And Biogen's position is that those publications
18 actually teach away from using DMF alone even for psoriasis,
19 let alone using 480 milligrams per day of DMF for treating MS.

20 First and foremost, neither one of them has anything
21 to do with MS. And for the reasons I discussed, one skilled in
22 the art would not believe you could extrapolate dosing from a
23 psoriasis teaching to another.

24 And, secondly, they specifically provide disclosures
25 about how mixtures of fumarates performed better than DMF used

1 alone. And excerpts from those publications are shown on
2 Slide 37. For example, Kolbach 1992, it noted that the
3 Fumaderm-type mixture it was using was significantly superior
4 to using DMF alone.

5 But, ultimately, the most important issue is that it
6 says nothing about MS. And even if you were to try to apply
7 the teachings to treating MS, you would have been led to use
8 the mixtures of Fumaderm of four active ingredients in doses up
9 to 1290 milligrams per day, similar to the conclusion that the
10 skilled artisan would have reached in looking at the Phase 2
11 study results.

12 Now, we heard this morning certain arguments about,
13 quote, optimization. I would like to just note that it's not
14 optimization to remove three active ingredients from a
15 four-active-ingredient mixture. That cannot constitute
16 optimization, to take out the three active ingredients that
17 were in the Schimrigk mixture.

18 It's not optimization to extrapolate one dosing
19 protocol from one disease to another. That's switching disease
20 categories entirely; that's not optimization. And it's not
21 optimization to disregard the express teachings of a reference
22 such as the Kappos 2 results and try to recalculate what they
23 specifically tell you the results were.

24 Your Honor, I'd like to touch briefly on one of the
25 additional items that they've mentioned, which is the WO '342

1 publication. We believe we will hear about that during this
2 case.

3 I think it's important to note that this patent
4 application was the subject of an interference with the '514
5 patent. The PTAB, the board of the patent office, found that
6 the WO '342 publication "Does not indicate 480 milligrams per
7 day as a therapeutically effective dose" for MS or any other
8 disease.

9 In addition, that then went on appeal to the federal
10 circuit. And the federal circuit agreed with the patent
11 office, agreed that the '342 publication did not disclose the
12 invention claimed in the '514 patent. So the federal circuit
13 looked at the '514 patent claimed invention and decided and
14 concluded that the WO '342 patent did not disclose that
15 invention.

16 In addition, the Court, in doing that analysis, noted
17 that "The prior art does not teach the key limitation of the
18 count, the 480-milligram daily dose."

19 So I think it's important to keep in mind that WO
20 '342 does not provide any motivation to test for 180 milligrams
21 per day for MS and let alone with any reasonable expectation of
22 success. And that issue has already been decided by both the
23 patent office and the federal circuit.

24 I'd now like to turn to Mylan's written description
25 of enablement tags.

1 First, as a reminder, the law is very clear that the
2 written description inquiry is whether the specification of a
3 patent describes the claimed invention such that a person of
4 ordinary skill in the art would understand that the inventor
5 was in possession of it at the time of filing.

6 Again, the focus is on the patent specification and
7 whether it provides support for what the inventor claimed. In
8 this case, each element of the asserted claims of the '514
9 patent is found and described in the written description of the
10 patent as part of an integrated whole. And we'll show that to
11 you, Your Honor.

12 This demonstrates that Dr. O'Neill was in possession
13 of the subject matter of the '514 patent claims at the time of
14 filing. That ends any reasonable inquiry under 35 U.S.C. 112.

15 As to enablement, the proper inquiry is whether one
16 of ordinary skill in the art reading a patent would be able to
17 "make and use the claimed invention without undue
18 experimentation."

19 That is clearly the case here. And as Mylan's
20 counsel noted, their positions or arguments with respect to
21 enablement are not really any different than their arguments
22 with respect to written description. And so we will only
23 spend -- I'll only spend a little bit of time on that this
24 morning.

25 But I'd first like to turn to the patent because

1 that's what we're supposed to focus on for the written
2 description analysis, not a lot of other information, which
3 I'll address shortly, Your Honor, that they pointed to. But
4 you have to look at the patent.

5 Mylan is correct that the '514 patent contains and
6 describes two groups of inventions. And we've color-coded
7 those. The purple methods, 1 through 3, represent the
8 screening method that Dr. Lukashev, which Mylan showed you
9 earlier, that he contributed to this patent. He was not a
10 clinician, and his focus was on the methods of screening for
11 compounds. And that is what this portion of the patent deals
12 with.

13 Shown in green are the claimed methods of treating
14 neurological diseases. And those are the parts of the
15 application that Dr. O'Neill contributed to. That is his
16 invention, is treating neurological diseases.

17 And it's not unusual for patents to contain
18 disclosures for two different inventions. It's not unusual for
19 the claims to change during the course of prosecution, to focus
20 on one invention or on another.

21 And it's a requirement that, if your claims do
22 change, that the subject matter of your claims changes, you
23 always need to make sure inventorship is correct; and,
24 therefore, you will need to file a correction of inventorship
25 and add an inventor to the claims -- to the patent or remove an

1 inventor if the claims changed such that the inventorship
2 changes.

3 In this case there are three claims, Your Honor, I'm
4 not going to talk about, Claims 17 to 19. Those are
5 Dr. Lukashev's -- those relate to Dr. Lukashev's aspect of the
6 patent, and therefore he's a proper inventor on this patent
7 because there are claims directed to portions of the
8 description that he contributed to.

9 The other claims are the method of treatment claims,
10 and those are Dr. O'Neill's invention.

11 Now, I'd like to note on Slide 42, right below the
12 disclosure of the five methods, it notes that in some
13 embodiments the neurological disease is MS or another
14 demyelinating neurological disease. So it's pointing out
15 specifically, and as a preferred neurological disease, that you
16 want to focus on MS or some other demyelinating neurological
17 disease. So even in this portion of the patent that's talking
18 about the methods, it's directing a skilled artisan in
19 particular to MS.

20 This is not surprising because, if you go to the very
21 beginning of the patent -- and I will note for Your Honor that,
22 when Mylan's counsel pointed to the beginning of the patent,
23 they skipped from paragraph 1 clear down to, like, paragraph 31
24 or 33. I've forgotten the exact paragraph. I think it was 31.
25 They left out this portion of the patent which is at the very,

1 very beginning.

2 Here at the very beginning of the patent it says, in
3 the very first substantive paragraph -- and I think this is
4 very important. The first paragraph is simply procedural
5 history of patent application filings, timeline of filings.
6 The first substantive paragraph says "Provided are certain
7 compounds for treating neurological diseases, including
8 demyelinating neurological diseases, such as, e.g., multiple
9 sclerosis."

10 So the first paragraph of the patent, at its time of
11 filing, said its focus is on treating multiple sclerosis. And
12 to further establish that, you only have to go to the very next
13 paragraph.

14 The very next paragraph, the patent goes on to
15 further explain multiple sclerosis and what it is, that it's an
16 autoimmune disease, and what its characteristics are, that "the
17 disease is characterized by inflammation in parts of the CNS
18 leading to the loss of the myelin sheathing around the neuronal
19 axons (demyelination), loss of axons, and the eventual death of
20 neurons."

21 For purposes of our discussion this morning, I'm not
22 going to get into what all of those things are other than to
23 say you'll hear testimony and evidence that those are
24 characteristics of MS. And so the patent is telling you that
25 the preferred focus of our treatment is MS and these are the

1 types of characteristics that we're focused on with respect to
2 MS for treating an MS patient.

3 And then if you go to Method 4 -- remember, there
4 were the five methods that I discussed earlier -- Method 4,
5 which is a method for treating a neurological disease by
6 administering to the subject at least one compound that is
7 structurally similar to DMF or MMF, that's found at the '514
8 patent at Column 3, lines 1 through 4. And the patent goes on
9 to discuss this method for -- in multiple places.

10 For example, if you look in the callout that's on the
11 left of this slide in the middle, it says "In some embodiments
12 Method 4 comprises administering an amount of at least one
13 neuroprotective compound having a formula" -- and it lists
14 several formulas. But then it stops and specifically points
15 out and puts in parentheses EG, DMF, or MMF.

16 So at this point the patent is specifically teaching
17 you that, for the method of treating MS, you should be using
18 DMF or MMF as a preferred way of treating the patient.

19 And I won't get into all of this this morning either,
20 Your Honor, but, as a point of reference, DMF is a compound
21 that, when you administer it to the patient, it very quickly
22 converts to MMF so that what is in the system of the patient
23 that's being -- having the effect is the MMF. And that is why
24 you'll see the patent is always referred to DMF or MMF to
25 ensure that it captures and protects this unique method of

1 using DMF to treat MS.

2 And if you then go to another portion of the patent,
3 which is shown at column -- shown on the last callout on the
4 left side, again, this is the patent saying that, for the five
5 methods, that neurological disease can also be multiple
6 sclerosis, calling that out again. But, more importantly, I'd
7 like to direct your attention to the callout on the right side
8 of this, Your Honor, where the Method 4 is being specifically
9 discussed. The patent specifically tells you again focus on
10 the DMF or MMF and to use a therapeutically effective amount of
11 that DMF or MMF.

12 And, again, right below that, it -- this is why we've
13 used the color-coding, Your Honor. Right below that in green
14 it's repeating again the same sort of characteristics that are
15 associated with MS and that the focus on using DMF and using a
16 therapeutically effective amount is on trying to impact those
17 characteristics of MS.

18 So then that takes you to the question of what is a
19 therapeutically effective amount?

20 Well, as shown in Slide 45, the '514 patent
21 specifically tells the skilled artisan. It says "A
22 therapeutically effective dose or therapeutically effective
23 amount is the amount of the compound which results in at least
24 one of prevention or delay of onset or amelioration of symptoms
25 of a neurological disorder in a subject, or an attainment of a

1 desired biological outcome, such as reduced neurodegeneration,
2 e.g., demyelination, axonal loss, and neuronal death."

3 So again, I'm repeating the same words over and over
4 again, Your Honor, but I think it's important to point out that
5 this same language is used throughout the patent as the
6 characteristics of MS and that the therapeutically effective
7 amount that is being taught here is that for treating MS.

8 I would then like to turn to what is meant -- what
9 the patent tells you is meant by the actual amount that you
10 should be using to treat a neurological disease.

11 If you look at Slide 46, this has a callout from the
12 patent, and you'll see in this paragraph that it says for the
13 Method 4 method of using DMF or MMF, that the effective amount
14 can range from at one point from 1 milligram to 50 milligrams
15 based on weight, and there's discussions about that.

16 But what's particularly important is it says "For
17 example, an effective dose of DMF or MMR" -- that was a typo,
18 Your Honor. Everybody agrees that should have been MMF -- "for
19 an effective dose of DMF or MMF to be administered to a subject
20 orally can be from about .1 gram to 1 gram per day" -- another
21 typo -- "200 milligrams to about 800 milligrams per day," and
22 then the patent puts in parenthetical and specifically directs
23 the skilled artisan to "e.g., from about 240 milligrams to
24 about 720 milligrams per day, or from about 480 milligrams to
25 about 720 milligrams per day, or about 720 milligrams per day."

1 So what you see here is a disclosure of nested ranges
2 where they're saying here's a broad range for neurological
3 diseases, and then it's focusing in onto these nested ranges
4 falling within each other. And the smallest range, the
5 narrowest range, is 480 to 720, and 480 is the lower dose --
6 the lowest dose of that nested range.

7 This would direct the skilled artisan that the most
8 preferred dose for purposes of the range showed in the 480 to
9 720 milligram range would be 480. It goes on to mention the
10 720-milligram-per-day dose.

11 Of note, Your Honor, contrary to the repurposing
12 arguments that we've heard today, the application, when it was
13 filed, Biogen was preparing for its Phase 3 studies. It knew
14 what it was testing; it knew what to describe. And that's
15 contained in the patent. And it includes the 480 linked to the
16 720-milligram-per-day dose that had shown efficacy in the
17 Phase 2 trial. So it was linking Dr. O'Neill's 480 to the 720
18 that showed efficacy in the trials.

19 Now, this represents all of the blaze marks that one
20 looks at for a written description analysis. The skilled
21 artisan would see that the patent was telling you MS was the
22 preferred disease to be treated, that DMF was the preferred
23 compound to use, and that you should be using 480-milligram per
24 day as the lowest dose of the narrowest range.

25 Now, Mylan has made several arguments this morning

1 about the FDA, about what Biogen commercial people thought, and
2 another -- the other Biogen patent application. Biogen
3 disputes each of these characterizations of the evidence, and
4 we'll discuss that in trial.

5 But, ultimately, they are all irrelevant to the 112
6 analysis. As I noted, what's relevant is what does one skilled
7 in the art believe when they read the patent? Do they believe
8 that the inventor was in possession of what was claimed? And
9 all of the blaze marks that I just identified to you, Your
10 Honor, lead the skilled artisan to believe that Dr. O'Neill was
11 in possession of 480 milligrams per day of DMF to treat MS.

12 With respect to enablement, again, I don't want to
13 spend too much time on that, but I do think it's important to
14 note, as shown on Slide 47, that the '514 patent also teaches
15 the skilled artisan how to make the formulation to use in the
16 claimed method.

17 Specifically, at Column 19, line 17 to 28, of the
18 patent, the '514 patent directs the skilled artisan to even
19 examples of formulations. It notes "Examples of some of the
20 formulations containing DMF and/or MMF are given in, e.g., U.S.
21 Patent Numbers 6,509,376, and 6,436,992."

22 So the '514 patent is telling the skilled artisan you
23 can make formulations to use in the claimed methods according
24 to these patents. We don't even think that disclosure was
25 necessary, that how to make a DMF-only formulation, a skilled

1 artisan would have known how to prepare. But, even then, the
2 patent is ensuring that the skilled artisan does know how to
3 prepare it.

4 So in conclusion for this morning, Your Honor, we
5 believe that the evidence that we'll present to you will
6 establish that the '514 patent embodied in Tecfidera should be
7 protected. The 480-milligram-per-day dose is not obvious over
8 the Biogen Phase 2 results, even if they were prior art. It's
9 not obvious over Schimrigk, a mixture of four active fumarates.
10 It's not obvious in view of the psoriasis art. And you can't
11 combine all those together through some sort of hindsight
12 approach to try to arrive at the claimed invention.

13 Because the art that they pointed to with respect to
14 102(b) -- just as a reminder, they've admitted that the Kappos
15 materials are 102(a). The 102(b) art, they're relying upon
16 Schimrigk. That's their primary reference, and they're trying
17 to combine that with the press release, which said very little
18 at all. Skilled artisan wouldn't know what exactly the results
19 were in that press release.

20 So their primary reference that says something in it
21 is Schimrigk. And, therefore, we contend that their
22 obviousness case, with respect to teachings regarding psoriasis
23 and with respect to Fumaderm and mixtures of fumarates, would
24 not render the claims obvious.

25 More importantly, even if there were a prima facie

1 case of obviousness, which there's not based upon the evidence
2 presented, Biogen has shown unexpected results with respect to
3 the 480-milligram-per-day dose, as I noted, Your Honor. It
4 exhibited an unexpected magnitude of efficacy. And, in fact,
5 Mylan likes to point to the fact that at one point, based on a
6 much more limited record, in an earlier IPR, the PTO found
7 prima facie case, but they also found unexpected results.

8 We, obviously, disagreed with the prima facie holding
9 based on that limited record before -- in an IPR proceeding;
10 but, ultimately, they concluded that there were unexpected
11 results shown by the 480-milligram-per-day dose.

12 And, finally, we will show that the baseline
13 imbalance argument is scientifically invalid. With respect to
14 the written description, as I just noted, we believe you'll
15 conclude, after all of the evidence, that the '514 patent
16 describes and enables the claimed method of treating MS.

17 One last item I'd like to note, Your Honor, there was
18 some reference during Mylan's opening argument to how certain
19 documents would, you know, mention other prior uses of
20 fumarates for other types of diseases, and they've tried to put
21 a lot of weight on that as if somehow the authors of those
22 publications were reaching conclusions that they could use the
23 teachings from those to inform their dosing decisions with
24 respect to MS.

25 There's no evidence of that, Your Honor. But,

1 rather, these are citations about how DMF had been used in
2 mixtures for long-term therapy. And, therefore, you do know
3 that, with mixtures of fumarates, that you do have safety and
4 tolerability. And it's reading way too much into those
5 cross-referencing without any evidence in support of that to
6 suggest that somehow those teachings matter to the dosing issue
7 that we have before, Your Honor.

8 With that, Your Honor, I'm done. Thank you.

9 THE COURT: Thank you very much.

10 If we recess for lunch now, how will we -- when we
11 resume, how will it go? You can start with -- okay.

12 MS. BLOODWORTH: Good morning. It's Ms. Bloodworth,
13 Shannon Bloodworth, for Mylan. We'll be calling Dr. Benjamin
14 Greenberg. And I expect that his direct testimony will be
15 quite lengthy.

16 THE COURT: The rest of the day?

17 MS. BLOODWORTH: Probably, yes, Your Honor. He'll be
18 testifying affirmatively on Mylan's affirmative case in chief,
19 and we'll likely be calling him back to reply on the unexpected
20 results.

21 THE COURT: I had understood that you would be doing
22 that.

23 So with regard to the schedule, if -- I don't know
24 what arrangements you all may have made for lunch. Are you
25 having something delivered here, or do you have other

1 facilities you're going to?

2 MR. MONROE: We have sandwiches in the conference
3 room, Your Honor.

4 MR. COPLAND: We have an arrangement made in the bank
5 building, Your Honor.

6 THE COURT: Oh, okay. You're in the bank building.
7 Again, I apologize for this. I wish it could be otherwise.

8 And then will 1:15 work for the arrangements that you
9 have?

10 MR. COPLAND: Yes, Your Honor.

11 THE COURT: Are you all ready to go until 5:00 today?
12 Is that how you expect to do it? No problem with that,
13 Mr. Copland?

14 MR. COPLAND: None, Your Honor.

15 THE COURT: The court stands in recess until 1:15,
16 and we'll resume with Mylan's case in chief, and the first
17 witness is Dr. Greenberg.

18 Thank you.

19 (Lunch recess taken, 12:16 p.m.)

20 THE COURT: Thank you. Please be seated.

21 I'm actually fine with you all submitting a thumb
22 drive of all the admitted exhibits at the end of the case for
23 purposes of the record. And then I understand you all submit
24 your own exhibits to the federal circuit, right?

25 MR. COPLAND: Yes.

1 THE COURT: Our clerk's office doesn't do that; is
2 that right?

3 MR. COPLAND: Yes, Your Honor.

4 THE COURT: Okay. Well, we're prepared to begin with
5 Mylan's case in chief. You may call your first witness.

6 MR. ANSTAETT: Your Honor, may I raise one issue?
7 Because I just want to make sure --

8 THE COURT: I have to find out where we are. We have
9 movable chairs here this afternoon.

10 MR. ANSTAETT: Your Honor, David Anstaett. I just
11 want to be crystal-clear on this because I don't want to screw
12 this up again, and I think I share this understanding with
13 opposing counsel. But that -- and this impacts disclosures
14 we're going to have to start making before we see Your Honor
15 again.

16 For cross-examination, you mentioned impeachment. My
17 understanding is the kind of litmus test is, if you're going to
18 use the adverse witness to try to get the document in evidence,
19 that has to be disclosed in advance. But beyond that --

20 THE COURT: This is not a criminal trial where we
21 surprise you on cross-examination with that criminal record
22 that nobody knew you had but we found it. That's true
23 impeachment. You don't have to disclose that ahead of time and
24 all that kind of stuff.

25 If I were going to default, I'd say disclose, both

1 sides. Just get it all out there. This is not a case about
2 surprise.

3 MR. ANSTAETT: Understood.

4 MR. FELDSTEIN: Your Honor, Mark Feldstein for Mylan
5 [sic]. I also don't want to screw up anything and just also
6 want to clarify, what was in the pretrial order for
7 cross-examination was that the parties agree that exhibits to
8 be used solely for impeachment and/or cross-examination need
9 not be included on a list of trial exhibits or disclosure in
10 advance of being used at trial.

11 What I understood Your Honor to clarify this morning
12 was, if you're going to try to admit it through the adverse
13 witness, however, is different and the only thing that
14 changes --

15 THE COURT: Part of your case in chief.

16 MR. FELDSTEIN: I'm sorry?

17 THE COURT: It would be part of your case in chief.

18 MR. FELDSTEIN: So the only thing that needs to be
19 disclosed for cross-examination is things that are going to be
20 admitted adversely.

21 THE COURT: I'm going to solve this problem for
22 everybody. That is no longer the operative rule. The rule
23 from now on is I want everything disclosed. Anything that you
24 are going to use, for impeachment purposes or otherwise, you
25 disclose to the other side.

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1 MR. ANSTAETT: That's fine, Your Honor. And I think
2 we can work with opposing counsel to figure out a schedule for
3 doing that.

4 THE COURT: Okay.

5 MR. FELDSTEIN: Thank you, Your Honor.

6 THE COURT: You have tomorrow to work it out.

7 MR. ANSTAETT: Understood, Your Honor. Thank you.

8 THE COURT: Thank you.

9 MS. BLOODWORTH: Thank you, Your Honor. With all
10 that out of the way, may I please call -- Mylan calls
11 Dr. Benjamin Greenberg.

12 THE COURT: Dr. Greenberg, would you please approach
13 the clerk, who will administer the oath to you before you take
14 the witness stand. Thank you.

15 THE CLERK: The witness is Dr. Benjamin Greenberg,
16 G-R-E-E-N-B-E-R-G.

17 **BENJAMIN GREENBERG, DEFENDANT'S WITNESS, SWORN**

18 DIRECT EXAMINATION

19 BY MS. BLOODWORTH:

20 Q. Good afternoon, Dr. Greenberg.

21 A. Good afternoon.

22 Q. Can you please state and spell your name for the record.

23 A. Benjamin Greenberg. B-E-N-J-A-M-I-N. Last name
24 Greenberg, G-R-E-E-N-B-E-R-G.

25 Q. Have you been retained as an expert witness in this case?

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1 A. Yes.

2 Q. By which party?

3 A. Mylan.

4 Q. And what is your area of expertise?

5 A. I'm a neurologist with a specialty in neuroimmunology.

6 Q. And could you please briefly describe for the Court your
7 educational background.

8 A. Certainly. I got my bachelor of arts in history in 1997
9 at Johns Hopkins University and at the same time received a
10 master's in microbiology and immunology at the Johns Hopkins
11 School of Public Health.

12 I received my medical degree at Baylor College of Medicine
13 in Houston, Texas, and went on to complete an internal medicine
14 internship in Chicago at Rush-Presbyterian-St. Luke's Hospital,
15 followed by my neurology residency at Johns Hopkins Hospital.

16 In 2005 to 2007, I was a postdoctoral research fellow in
17 microbiology and immunology at the school of public health and
18 at the same time joined the faculty of the department of
19 neurology at Johns Hopkins, achieving the rank of assistant
20 professor before transitioning to my current place of
21 employment, the University of Texas, Southwestern, in Dallas,
22 Texas, where I'm currently a professor within the department of
23 neurology.

24 Q. And what is your current clinical positions at the
25 University of Texas, Southwestern?

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1 A. So, currently, clinically I direct the multiple sclerosis
2 center, the transverse myelitis and neuromyelitis optica
3 program, as well as the pediatric multiple sclerosis and
4 neuroimmunology program called the CONQUER program.

5 Q. Do you have any current -- currently have any
6 administrative roles?

7 A. I serve as the fellowship director for both the autoimmune
8 neurology and multiple sclerosis program at the university.
9 I'm the section head for the section of neuroimmunology. I
10 serve as the vice chair of research for the department of
11 neurology and neurotherapeutics, and I direct a center called
12 Neurosciences Translational Research Center, which is part of
13 our Brain Institute.

14 Q. And do you currently hold any board certifications?

15 A. I do. I'm currently certified by the American Board of
16 Psychiatry and Neurology, and I have a separate certification
17 in rare neuroimmunologic disorders.

18 Q. Do you currently treat patients with multiple sclerosis?

19 A. I do.

20 Q. And I'll refer to that often as MS, if it's okay.

21 A. Fine by me.

22 Q. And, approximately, how many patients do you treat with
23 MS?

24 A. On average, around a thousand in a year.

25 Q. And do you prescribe any medications to your patients with

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1 MS?

2 A. I do.

3 Q. And approximately how many medications do you prescribe?

4 A. There are different types of medications we use. The ones
5 that are indicated to treat multiple sclerosis, anywhere from
6 15 to 20 different medications.

7 Q. Are you a member of any neurology or MS research
8 organizations?

9 A. I am. I am currently a fellow in the American Academy of
10 Neurology, a fellow in the American Neurological Association,
11 and I'm a member of the Texas Neurological Society.

12 Q. Have you served as a -- in an editorial capacity on any
13 journals relating to MS or neurology?

14 A. I have. I was a section editor for JAMA Neurology and
15 have been a reviewer for a number of different journals,
16 including the Journal of Immunology and the Multiple Sclerosis
17 Journal.

18 Q. Have you authored any abstracts that have been presented
19 at scientific meetings?

20 A. I have.

21 Q. Approximately how many?

22 A. At this point probably over 50.

23 Q. And have you served as a principal investigator for any
24 clinical trials?

25 A. I have.

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1 Q. And what type of clinical trials?

2 A. Both observational and interventional trials, and amongst
3 the interventional trials these have included Phase 1, Phase 2,
4 and Phase 3 trials.

5 Q. We're going to hear about these terms a lot today. So
6 maybe we could just -- could you just briefly describe what a
7 Phase 2 clinical trial generally is?

8 A. Certainly. So in the various phases of clinical trials,
9 they each have different goals, different roles to play. The
10 Phase 2, being the middle of the three phases, is there both to
11 look at the safety of an agent to help define dose ranges that
12 may be useful in treating a disorder and to determine early on,
13 usually in a small cohort over a short period of time, is there
14 enough of an efficacy signal to move forward with regulatory
15 requirements for larger trials.

16 Q. And then what is a Phase 3 clinical trial generally?

17 A. Generally, a Phase 3 trial is a much larger trial that's
18 used by regulatory agencies, such as the FDA or the European
19 EMA, to show that an agent is both safe and effective in the
20 population that you're targeting in order to gain regulatory
21 approval for the purposes of marketing a drug within the U.S.
22 or elsewhere in the world.

23 Q. And if you could turn in your binder to DTX 1636, and
24 we'll also put it up on the screen.

25 Is DTX 1636 an accurate copy of your curriculum vitae?

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1 A. It is, at the time of submission. The only thing that
2 will be updated is I did give two talks last week that aren't
3 on here. One was in Ireland, and one was in London, neither of
4 which had anything to do with multiple sclerosis. They were
5 related to a different condition.

6 MS. BLOODWORTH: Okay. And, Your Honor I move to
7 admit DTX 1636.

8 MR. FELDSTEIN: No objection, Your Honor.

9 THE COURT: I think under the -- we had agreed that,
10 where there was no objection, they would just come in. So,
11 yes, admitted.

12 But if you don't want to take up the time on it and
13 you know that there's no objection, I'm happy to let it just
14 come in. You can just say this is without objection.

15 MS. BLOODWORTH: Thank you, Your Honor. We disclosed
16 all of the exhibits last night. So thank you.

17 (DTX 1636 was admitted.)

18 BY MS. BLOODWORTH:

19 Q. Now, Dr. Greenberg, you've submitted two expert reports in
20 this case, correct?

21 A. Yes.

22 Q. And, generally, what are your -- what are the opinions
23 you're going to be presenting to the Court during your
24 testimony?

25 A. So today we're going to be talking about two opinions.

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1 The first has to do with obviousness, and the second relative
2 to no written description or enablement.

3 Q. And if we -- let's start with your obviousness opinions.
4 Dr. Greenberg, have you set out a pathway for why the asserted
5 claims are obvious?

6 A. Yes.

7 Q. Okay. And what are those pathways?

8 A. There is a variety, as shown on the screen, looking at
9 prior art before the priority date, including the January 2006
10 press release from Biogen reporting the results of a Phase 2
11 study, as well as an abstract published by Schimrigk in 2004
12 which reported the impact of using dimethyl fumarate in a
13 multiple sclerosis population in a variety of doses and showing
14 efficacy.

15 Beyond that, we look at the Kappos 2006 presentation in
16 combination with the Schimrigk 2004 abstract; the Kappos 2006
17 abstract in combination with the Schimrigk 2004 abstract; the
18 Kappos 2006 abstract along with WO '342; and, ultimately, the
19 Kappos 2006 abstract combined with the clinical trials
20 document, the Joshi '999 patent, and the ICH guidelines.

21 Q. So we'll get there. We'll work through those.

22 Can we take a step back and just -- can you describe what
23 is MS, if we can go through a little bit of the background of
24 the disease here.

25 What is MS?

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1 A. Certainly.

2 Multiple sclerosis is when two different parts of the body
3 intersect. And we have to explain each individually.

4 So most of the time multiple sclerosis very appropriately
5 is defined as a neurologic disorder because that's the part of
6 the body that gets damaged. And the nervous system is what
7 allows your brain to connect to your body and your body to
8 connect to the brain. And those connections are, as depicted
9 on the screen, these neurons with coated wires.

10 The coating around the wires is called myelin. And that
11 coating on the wires is very similar to a speaker wire that you
12 would see in a stereo, so connecting a stereo to a speaker
13 where you want to listen to the music. And you would turn on
14 the power of the stereo and transmit a signal, and you'd hear
15 the music.

16 If you were to fray the insulation of that speaker wire,
17 the music wouldn't sound so good. The signal wouldn't get
18 through. And, as depicted here on the screen, in multiple
19 sclerosis, we see damage to that myelin. We see fraying of the
20 insulation around the wires such that the signal doesn't get
21 through.

22 If that fraying happens to the wire that controls your
23 right hand, you have difficulty controlling your right hand.
24 If it happens to the wire connecting your eye to your brain,
25 you have blurred vision. So the symptom an individual with

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1 multiple sclerosis has depends on which wire gets damaged.

2 But critical to our understanding of multiple sclerosis
3 and why we don't just consider it a neurologic disease, we
4 consider it an autoimmune disease, is based in how the damage
5 occurs. So why does a person with multiple sclerosis get
6 damage to those insulated wires? And that's where the immune
7 system comes in.

8 Q. And so what is the immune system?

9 A. So the immune system represented here graphically in a
10 very basic but fun way is your body's defense system, a variety
11 of cells that are there to combat the ongoing onslaught of
12 viruses and bacteria that try to get into our body every day of
13 the week, every week of the year.

14 And the immune system has evolved over thousands and
15 millions of years to have lots of specialized parts of the
16 immune system to handle all the different types of invaders we
17 might be exposed to. On some days, it's a virus; on other
18 days, it's a bacteria. Sometimes it's a parasite; sometimes
19 our immune system is fighting cancer. So there's been an
20 evolution of that immune system to fight off these different
21 invaders.

22 The best analogy I use for the immune system, when talking
23 with patients or families about it, is to compare it to a herd
24 of cats, strangely enough. So if you'll indulge me, cats,
25 fascinating animals. They are genetically engineered to chase

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1 mice, chase bugs. So if you have a cat, and a mouse enters
2 your home, odds are the cat is going to eat or chase away the
3 mouse.

4 And hundreds of years ago, before we had Orkin and
5 pest-control companies, we domesticated a house and called it a
6 house cat. And that cat was there to walk around our home all
7 day long and protect us from foreign invaders.

8 Fast forward to the 21st century, and sometimes a few of
9 our domesticated cats can get confused and think the drapes or
10 the power cords or the sofa looks like a mouse tail and, by
11 mistake, chew on the home that it's supposed to be defending.

12 That same event can happen within the immune system.
13 Sometimes a breed of cat, Siamese, can get confused about
14 something in the house and be convinced it looks like a virus
15 or bacteria and chew on that target, causing damage. And
16 that's the definition of autoimmunity, a immune system -- a
17 part of an immune system that thinks it's doing its job but has
18 the wrong target.

19 And when we take all autoimmune diseases and we put them
20 together, immunologically, we separate them by two features:
21 which breed of cat gets confused, and what are they confused
22 about.

23 So if you have a certain breed of cat confused about one
24 part of the house, that's one autoimmune disease. If that same
25 breed of cat is confused about a different room in the house,

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1 we classify it differently, but it's still the same part of the
2 immune system that's getting confused.

3 And so when we talk about treating autoimmunity, we focus
4 on which part of the immune system has gotten confused to a
5 significant degree as much or more than what are they confused
6 about.

7 Q. And so what causes the confusion in MS?

8 A. So we have a lot of theories as to what triggers the
9 confusion, but we have a lot of data over time to suggest which
10 breed of cat has gotten confused.

11 And as we've heard about, multiple sclerosis is a
12 complicated condition, and I 100 percent agree. So if I take
13 the population of multiple sclerosis patients as the million or
14 so in the United States with multiple sclerosis, there's
15 multiple different probable types of MS, meaning, for a lot of
16 the patients, it may be the Siamese cat. And for another
17 group, smaller group, it might be the tabby cat.

18 So there are lots of ways to get to the end organ damage.
19 But over the decades, a wealth of data was generated to suggest
20 that a large part of the population had a derangement in a
21 certain breed, a certain type of cat. And that captured the
22 attention of most of the field for over 20 years. And that's
23 depicted here on this slide which is Slide Number 10.

24 And it was referenced in the opening, this notion of Th1
25 and Th2 cells. So a T cell is a cat that can have multiple

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1 different breeds. And depending on the environment it lives in
2 and what it's being asked to do, it can differentiate into a
3 Th1 or Th2 cell. And they have different properties, and they
4 fight off different infections.

5 In the setting of autoimmunity, in some conditions, it's
6 the Th1 population of cells that expands and ultimately leads
7 to the damage. And that's what we've found in multiple
8 sclerosis and psoriasis.

9 So while the cats of multiple sclerosis are confused about
10 the brain and spinal cord -- and in psoriasis, they're confused
11 about the skin -- it's the same breed of cat that ultimately
12 needs to be controlled.

13 And the way you control it -- and what was found through
14 scientific studies as well as clinical trials -- was that, if
15 you could expose individuals with these diseases to medications
16 that would shift the cats from that Th1 aggressive immune cell
17 into a Th2 profile, you would essentially put the patient into
18 remission.

19 Q. So does it matter what organ is being targeted in the
20 immunomodulation?

21 A. So we always pay attention to what organ is being targeted
22 around designing clinical trials and looking at outcome
23 measures. But when we're talking about modulating an immune
24 system that is flowing through our blood, whether the confused
25 cat is going to wind up in the brain or the skin, it still

1 needs to be retrained.

2 So we group them, from a therapeutic perspective, based on
3 which arm of the immune system is confused more so than what
4 the end organ target of that confusion is.

5 Q. And you had mentioned remission in Slide 10. I'm used to
6 hearing that in the context of cancer.

7 What does that mean in MS?

8 A. So remission, as you state in the context of cancer, is
9 defined when we have no further evidence of cancer cells. In
10 multiple sclerosis, we don't have the same type of testing that
11 we have in cancer or other diseases like diabetes or
12 hypertension.

13 So remission is defined by a lack of new relapses or using
14 a surrogate measure that we've developed over time, and that's
15 the MRI. So we look for evidence that an intervention leads to
16 an improvement in these features.

17 Q. And what tools do clinicians use to get patients into
18 remission?

19 A. So these tools are globally defined as disease-modifying
20 therapies. You'll sometimes, if it gets late today and I'm
21 going too fast, I may say DMT. It stands for disease-modifying
22 therapy. And that's to distinguish the interventions that are
23 targeting the immune system and inducing remission from other
24 medications I might prescribe to treat symptoms of an MS
25 patient.

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1 Q. How do you know whether secondary prevention measures are
2 working?

3 A. So in multiple sclerosis, as in all conditions where we
4 use a disease-modifying therapy to prevent a future outcome,
5 which is this notion of secondary prevention, much like in a
6 diabetic if I want to prevent a heart attack or a stroke, I
7 manage their blood sugar. So by managing their blood sugar, I
8 am preventing a secondary outcome. In multiple sclerosis, by
9 managing the immune system, I am preventing relapses or
10 disability.

11 And so when we're talking about secondary prevention, we
12 have to recognize we use surrogates along the way to predict
13 that ultimate outcome. So in the example of multiple
14 sclerosis, the surrogate that we use is MRI activity. Does
15 preventing activity on an MRI have any direct benefit to a
16 patient?

17 That actually hasn't been proven in the moment. You can
18 have asymptomatic lesions on MRI. But we know, by changing the
19 MRI, we are going to prevent downstream ultimate disability or
20 symptoms in the future. And so, similar to other conditions,
21 that's the goal of a disease-modifying therapy.

22 Q. And who does MS affect?

23 A. So the most common individual demographically who would be
24 affected by multiple sclerosis is usually young women. So it's
25 about 3 to 1 women to men, and the average age of diagnosis is

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1 about 30 years of age.

2 Q. Thank you. Now, let's turn to your obviousness opinions
3 in this case.

4 A. And I forgot to mention, as we were talking about the
5 Th1/Th2 pathway, it's just worth noting -- and I spoke to
6 this -- that the activation of the T cell in autoimmunity, as
7 I'm pointing on Slide 11, happens in the periphery. And then,
8 once activated, that confused cell crosses over into the
9 central nervous system to cause the damage.

10 I could just as easily swap out "central nervous system"
11 to "skin" to represent psoriasis. But the immune system and
12 the activation is living in the blood and flowing to the end
13 organ that's going to be targeted.

14 Q. Thank you.

15 Dr. Greenberg, in creating your obviousness opinions, did
16 you define what a person of ordinary skill in the art is?

17 A. Yes.

18 Q. And what is your definition of a person of ordinary skill
19 in the art?

20 A. And it's worth noting at the outset, my understanding is
21 there were different definitions between Mylan and Biogen. And
22 this has been the accepted, which I agree with, that you hold
23 at least a medical degree, at least three years of training in
24 neurology, and at least three years of clinical experience
25 treating multiple sclerosis patients.

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1 Q. Do your opinions differ whether you used one definition or
2 the other in the case?

3 A. No.

4 Q. Did you consider the level of ordinary skill in the art
5 from a particular time period?

6 A. Yes.

7 Q. And was that around February 8, 2007?

8 A. Yes.

9 Q. And do you understand what factors are considered when
10 evaluating obviousness?

11 A. Yes.

12 Q. And what are they?

13 A. You have to consider the scope and content of the prior
14 art, what's available prior to that important date, the
15 difference between the claimed invention in the prior art to
16 see if there is something uniquely different between what's in
17 the patent versus what's in the prior art, the level of
18 ordinary skill in the art, and then secondary considerations of
19 nonobviousness.

20 Q. And we're going to hold on the secondary considerations of
21 nonobviousness for today.

22 Do you understand that obviousness must be found here by
23 clear and convincing evidence?

24 A. Yes.

25 Q. And did you use this standard when assessing the

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1 invalidity of the asserted '514 patents?

2 A. Yes.

3 Q. Let's turn to the asserted claims if we can.

4 Are you aware that the asserted claims in this case are
5 Claims 1 through 4, 6, 8 through 13, 15, and 16 of the '514
6 patent?

7 A. Yes.

8 Q. Okay. And looking at representative independent Claim 15
9 on Slide 14, what elements does it require?

10 A. So this claim requires a treatment for multiple sclerosis
11 with a therapeutically effective amount of dimethyl fumarate in
12 a dose of about 480 milligrams per day.

13 Q. And have you prepared a slide of the representative
14 dependent claims in this case?

15 A. Yes.

16 Q. And turning to Slide DDX 1100.15, what are those
17 additional representative dependent claims?

18 A. As listed here, Number 2 indicated specifically a tablet,
19 a suspension, or a capsule.

20 Dependent Claim 3 specified separate administrations of
21 two, three, four, or six equal doses.

22 Dependent Claim 4 specified separate administrations of
23 two equal doses.

24 And dependent Claim 8 specified administered to the
25 subject for at least 12 weeks.

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1 Q. Is two equal doses often referred to as BID dosing?

2 A. Yes.

3 Q. And did you create a slide summarizing your opinions?

4 A. Yes.

5 Q. And let's turn to Slide 16. What is your opinion about
6 whether or not the '514 patent asserted claims are obvious?

7 A. So, first, I think it's important to note that DMF,
8 dimethyl fumarate, was known in the prior art to treat multiple
9 sclerosis. There had been two different studies published in
10 the prior art showing that it was an effective therapy for
11 multiple sclerosis, the disease that we're specifically
12 targeting here.

13 Furthermore, those prior arts indicated that a dose range
14 between 360 milligrams and 720 milligrams was effective.

15 Thirdly, in that analogous autoimmune disease with the
16 same type of confused-cat psoriasis, there had been studies
17 showing specifically 480 milligrams of dimethyl fumarate a day
18 could shift those cats and lead to a clinical benefit in those
19 patients with psoriasis.

20 Fourthly, the prior art taught that three-times-a-day
21 dosing, sometimes called TID dosing, was not necessary to
22 maintain efficacy, thus an artisan would be free to use BID or
23 twice-daily dosing.

24 And, finally, a person skilled in the arts would be
25 motivated and would have a reasonable expectation of success in

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1 treating multiple sclerosis patients with 480 milligrams a day
2 of dimethyl fumarate.

3 Q. So let's start going through the background of the art.

4 You stated that the DMF was already known to treat MS and
5 that was disclosed in the art. On what references did you rely
6 on for that opinion?

7 A. So the first reference, as shown here on Slide 17, is a
8 January 2006 press release which came from Biogen Idec
9 announcing the results of a Phase 2 trial using dimethyl
10 fumarate to treat multiple sclerosis.

11 Q. And we'll hear more about that trial a little bit later,
12 but were there any other references that were known in the art
13 that taught the treatment of dimethyl fumarate for treating MS?

14 A. Yes.

15 Q. And what were those?

16 A. So the next piece of art that was available would be the
17 '376 patent, shown here on the Slide 18.

18 Q. And that's DTX 1000 for the record.

19 And what did the '376 patent teach a skilled artisan about
20 whether DMF was known for treating multiple sclerosis?

21 A. So, as outlined here, it indicated that one or more
22 diethyl fumarates could be used for the therapy of autoimmune
23 diseases such as -- and it included multiple sclerosis and
24 specifically indicated dimethyl fumarate as an agent.

25 Q. And when was the '376 patent filed?

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1 A. The date of the patent is January of 2003, with a filing
2 much smaller on my screen, but --

3 Q. Let me see if we can make that bigger.

4 A. -- I'm happy to see it larger.

5 It looks like October 29th, 1999.

6 Q. Great. And you mentioned that it issued in January 21st,
7 2003. What did the '376 patent claim?

8 A. So the '376 patent claimed that you could use a
9 preparation of dimethyl fumarate to treat autoimmune diseases
10 such as multiple sclerosis.

11 Q. So what did the '376 patent generally teach the skilled
12 artisan as of the priority date of the '514 patent?

13 A. So the '376 patent teaches a skilled artisan that this
14 agent could be used to shift autoimmune diseases, linking -- it
15 goes on to link -- psoriasis and multiple sclerosis in the same
16 list, indicating it would effectively treat individuals with
17 these types of autoimmune diseases.

18 Q. Did the '376 patent also teach that the pharmaceutical
19 preparations could be either a tablet or a capsule and include
20 excipients?

21 A. Yes.

22 Q. And is there any other references you relied upon for your
23 opinion that DMF was already known to treat multiple sclerosis
24 in the prior art?

25 A. Yes.

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1 Q. And what is that reference?

2 A. So the next reference would be the '999 patent. I
3 sometimes refer to it as the Joshi '999 patent.

4 Q. And that is DTX 1001 for the record.

5 And did you review the 999 patent as a prior art reference
6 in this case?

7 A. Yes. The filing date was July 17th, 2002.

8 Q. And what was the number of the patent application?

9 A. The patent application was 10,107,077. That was the
10 original filing. And the one we're referring to here is
11 7,320,999.

12 Q. And do you know when the patent published, the PCT
13 application published?

14 A. So the publication date, the date of patent listed here is
15 January 22nd -- oh, excuse me. We may need to blow it up.

16 Q. It's in the upper left.

17 A. So we have a filing date, and then --

18 Q. And I was asking about the prior publication date. Do you
19 know when --

20 A. Listed here as January 23, 2003.

21 Q. And when did the '999 patent issue?

22 A. As listed there, January 22nd, 2008.

23 Q. And if we could look at Claim 1 of the DTX 1001 patent.
24 What does it claim?

25 A. So I think we'll put it up on the screen.

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1 Q. It's page 7, Column 8.

2 A. So the '999 patent claims in Claim 1, "A method of
3 treating multiple sclerosis using a pharmaceutical preparation
4 effective for treating said multiple sclerosis wherein the only
5 active ingredient for the treatment of multiple sclerosis is
6 dimethyl fumarate."

7 Q. Is the claim limited to any specific formulation of
8 dimethyl fumarate?

9 A. No.

10 Q. And what did the '999 patent generally teach the skilled
11 artisan as of the priority date of the '514 patent?

12 A. So this teaches the artisan that dimethyl fumarate as a
13 monotherapy could be used to treat multiple sclerosis.

14 Q. And so if we can turn back to the slides, on Slide 20
15 we're going to look at the '514 patent again.

16 And so we've gone over the treatment of dimethyl fumarate
17 for multiple sclerosis. And let's focus on the remaining
18 element, which is the 480-milligram dosing.

19 Did you make a demonstrative to give an overview of the
20 prior art?

21 A. Yes.

22 Q. And turning then to Slide 22, what does Slide 22 show?

23 A. So Slide 22 is a timeline. It places the February 8th,
24 2007, critical date on the far right. And then it shows
25 publications that go back approximately 17 years relative to

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1 dimethyl fumarate and autoimmune diseases and dosing.

2 Q. And we talked about, on the upper right-hand corner, the
3 January 2006 press release.

4 A. Yes.

5 Q. Which that was the announcement of the Phase 2 clinical
6 trial using DMF for treating multiple sclerosis?

7 A. It was the announcement of the results of that trial, yes.

8 Q. And that was DTX 1136 for the record.

9 And so let's look at the far left-hand corner and go back
10 to 1990. What did the Nieboer -- what is the Nieboer 1990
11 reference?

12 A. So the Nieboer 1990 reference is to a published paper
13 entitled "Fumaric Acid Therapy in Psoriasis: A
14 double-Blind Comparison Between Fumaric Acid Compound
15 Therapy and Monotherapy with Dimethylfumaric Acid Ester."

16 It was published by Nieboer and colleagues in the journal
17 Dermatologica in 1990.

18 Q. For the record it's JTX 2179.

19 What does the Nieboer 1990 reference teach a skilled
20 artisan?

21 A. So there are several important things that come out of the
22 Nieboer 1990 article. The first, as was discussed earlier
23 today, there is this notion of Fumaderm, which is a medication
24 that's approved in Germany for psoriasis that is listed to have
25 four active agents. There's been some discussion on how this

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1 is different, if at all, from one of those four agents,
2 dimethyl fumarate.

3 And Nieboer and colleagues in 1990, in a study of
4 approximately 45 patients with psoriasis, set out to compare
5 this notion of whether or not dimethyl fumarate was the active
6 agent from an immunologic point of view relative to this
7 autoimmune disease.

8 And so they took patients and they were separated into two
9 groups: one who received dosing of dimethyl fumarate as a
10 monotherapy and one group who received essentially Fumaderm,
11 which is labeled as FAC.

12 And they looked to see if there was efficacy and safety of
13 these agents and to ask the question what dose would work and
14 was there actually a difference between DMF as a monotherapy or
15 when it's combined with the three other agents in the Fumaderm
16 label.

17 Q. And what did the Nieboer 1990 reference conclude about
18 whether or not DMF monotherapy -- about the activity of DMF
19 monotherapy with the Fumaderm combination?

20 A. So what they concluded in this clinical trial was that
21 dimethyl fumarate was the active agent; that, immunologically,
22 the efficacy that patients experienced was being dictated by
23 how much dimethyl fumarate they were exposed to and not how
24 much Fumaderm as a whole they were exposed to.

25 Q. And where in the Nieboer 1990 reference do you point to

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1 for that conclusion?

2 A. So if you turn to Slide 24, DDX 1124, what you see is a
3 paragraph that talks about the conclusions. And this has led
4 to some concern about the labeling. But in the end what they
5 say in the abstract and later is that 480 milligrams of DMF
6 given as 240 milligrams twice a day was effective for treating
7 psoriasis.

8 Q. And just so the record's clear, I think you might have had
9 a little mistake in the slide numbers.

10 So Slide 23 is the Nieboer 1990 reference?

11 A. Slide 23. Excuse me.

12 Q. That's okay.

13 And, again, the conclusion was that --

14 A. That 480 milligrams a day was effective.

15 Q. And how frequently was the DMF dosed in that study?

16 A. So it was dosed in two equal doses, BID dosing of
17 240 milligrams in each dose.

18 Q. So now we've mentioned Fumaderm. And can you explain
19 again, what is Fumaderm and how does Fumaderm relate to DMF
20 monotherapy?

21 A. So Fumaderm had been around for many years and
22 historically was compounded between four different agents. And
23 for historical reasons and for ease, because it was available,
24 was used in psoriasis for many years and led to approval for
25 its use in Germany for psoriasis.

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1 Over time, there was evidence mounting, both from basic
2 science studies, studies with cells from human beings, and
3 ultimately clinical trials, that teased out the fact that,
4 despite historically combining these four agents, the
5 immunologically active molecule was dimethyl fumarate.

6 And that became the accepted understanding within the
7 world of autoimmune diseases, leading to studies such as this
8 to prove it and then ultimately taking it almost for granted, I
9 should say, that DMF was the active agent in Fumaderm.

10 Q. I think you've heard reference, though, that there's
11 other, quote, active, end quote, agents in Fumaderm.

12 As of 2006 or '7, did the skilled artisan still believe
13 that there was any substantive difference between DMF and
14 Fumaderm?

15 A. From an immunologic activity perspective, no. I think
16 it's important to note that, when we're using the terms
17 "active" in a patent, we're separating it from excipients. But
18 in the world of skilled artisans looking to treat patients, the
19 art had already separated out that the clinically active, the
20 immunologically active molecule of Fumaderm was only dimethyl
21 fumarate.

22 Q. Was there another paper that you relied upon that also
23 noted the activity of dimethyl fumarate in Fumaderm?

24 A. Yes.

25 Q. And what was that paper?

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1 A. So this is a paper authored by Kolbach and colleagues in
2 1992.

3 MS. BLOODWORTH: And for the record, the Kolbach 1992
4 paper is JTX 2178.

5 BY MS. BLOODWORTH:

6 Q. What does Kolbach 1992 teach the skilled artisan?

7 A. So Kolbach published a paper entitled "Fumaric Acid
8 Therapy in Psoriasis: Results and Side Effects of Two Years of
9 Treatment."

10 So this is a longer study looking, again, at the question
11 that was posed in Nieboer as to whether or not dimethyl
12 fumarate and at what dose would effectively treat the
13 autoimmune disease psoriasis.

14 Q. And Biogen claims, actually, that Kolbach says that DMF is
15 not the active ingredient.

16 Do you understand that argument?

17 A. I do.

18 Q. Do you agree with it?

19 A. No.

20 Q. Why not?

21 A. I think it misstates what the authors came to conclude.
22 And I understand where the confusion comes from, and I think I
23 can clarify.

24 Q. Please do.

25 A. In the paragraph that's on the screen here, which is

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1 DDX 1100, Slide 24, the first sentence of the paragraph says
2 "FAC treatment was significantly superior to DMF."

3 And reading that in isolation, without context of the
4 entire article, the structure of the trial, or the conclusions,
5 I could understand how one would read that to assume that
6 Fumaderm was a better agent than dimethyl fumarate.

7 But what Kolbach and colleagues are referring to in this
8 sentence are the treatment arms in the trial, not the agents.
9 So when patients came into the trial, they either received
10 dimethyl fumarate on its own as 240 milligrams or they received
11 Fumaderm up to a dose that delivered 480 milligrams of dimethyl
12 fumarate. So when we're looking at the two arms, what's called
13 the Fumaderm arm had double the dose than the dimethyl fumarate
14 arm.

15 So in this sentence, when they say "FAC treatment was
16 significantly superior to DMF," they're saying the arm that
17 received Fumaderm did better, and they go on to clarify that
18 the amounts of DMF in the FAC therapy were twice that of DMF,
19 and, apparently, a dosage of 480 milligrams of dimethyl
20 fumarate per day is necessary to achieve a satisfactory
21 improvement in approximately 50 percent of patients.

22 And it's in this sentence that we really see how skilled
23 artisans in the time came to recognize DMF was the active
24 agent. They don't refer to the dose of Fumaderm they received
25 in milligrams; they refer to that arm based on how many

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1 milligrams of DMF they were exposed to.

2 Q. And so what does the Kolbach 1992 reference teach the
3 skilled artisan?

4 A. So there are several takeaways from the Kolbach paper.
5 The first is the generally accepted view that, when looking at
6 Fumaderm literature, you report it based on how much dimethyl
7 fumarate the patient is exposed to, so much so that they start
8 referring to milligram doses not relative to Fumaderm but
9 relative to DMF.

10 Secondly, you find that, over a longer-term study in an
11 autoimmune disease, you found an effective therapy for that
12 confused immune system. And that was found by dosing
13 480 milligrams a day of dimethyl fumarate.

14 Q. And what did Kolbach report about the efficacy on
15 psoriasis?

16 A. Kolbach concluded that it was, at that dose, an
17 efficacious therapy for that autoimmune disease.

18 Q. Now, did you make a summary slide of additional references
19 that go through and equate the DMF in Fumaderm with the active
20 component of Fumaderm?

21 A. Yes.

22 Q. If we could turn to Slide -- DDX 1100, Slide 25.

23 What is on Slide 25, Doctor?

24 A. So the literature has numerous articles that explore the
25 relationship of DMF to Fumaderm and explore the fact that the

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1 immunologically active agent within Fumaderm was DMF. And, as
2 outlined, here are four representative articles from the
3 literature ranging from 1993 to 2004 with conclusions from each
4 of the papers.

5 Q. And looking first at the Nibbering 1993 article, which is
6 JTX 2216, what does the JTX 2216 teach a skilled artisan?

7 A. So the Nibbering 1993 article indicated that MMF -- and,
8 as we heard today, this is the active metabolite of DMF -- is
9 the most active metabolite of the new antipsoriasis drug
10 Fumaderm.

11 Q. Turning to the next, de Jong 1996, which is JTX 2204, what
12 did that article teach a skilled artisan?

13 A. So in 1996 de Jong wrote that the most effective fumarate
14 metabolite of Fumaderm is monomethyl fumarate, which is formed
15 in the circulation by hydrolysis of dimethyl fumarate.

16 Q. What did de Jong 1996 teach the skilled artisan?

17 A. So de Jong taught that, even though we are giving an
18 agent, Fumaderm, that has four different compounds in it, what
19 is effectively impacting the human being is the metabolite of
20 dimethyl fumarate and it doesn't recognize activity -- doesn't
21 note any activity coming from the other three agents that are
22 represented in Fumaderm.

23 Q. Turning to the third article, the Ockenfels 1998, which is
24 JTX 2233, what did the Ockenfels article teach a skilled
25 artisan in 2004 about the activity of DMF?

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1 A. So Ockenfels is in 1998.

2 Q. 1998. Excuse me.

3 A. In 1998 noted that dimethyl fumarate, which is metabolized
4 to monomethyl fumarate, is apparently the most potent
5 antipsoriatic substance in Fumaderm.

6 Q. The last article, turning to Ormerod 2004, which is
7 JTX 2218, again, what did the Ormerod article teach the skilled
8 artisan about the activity of DMF in 2004?

9 A. So in 2004 Ormerod noted "There is cumulating evidence
10 that dimethyl fumarate, the main ingredient of Fumaderm, is the
11 active compound."

12 Q. And so, as of the priority date in this case,
13 Dr. Greenberg, what is your opinion about whether or not it was
14 established, as of the priority date, that DMF was the active
15 component in Fumaderm?

16 A. I think it was firmly established within the literature
17 that dimethyl fumarate was the active substance,
18 immunologically speaking, in Fumaderm, so much so that the
19 literature would refer to Fumaderm based on how many milligram
20 of dimethyl fumarate a patient got.

21 Q. As opposed to how much was totally administered in the
22 pill, they would only talk about how many milligrams of
23 dimethyl fumarate they received; is that right?

24 A. Correct. So, if somebody was taking six pills of
25 Fumaderm, if I was reporting the milligrams of Fumaderm they

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1 received, you would see a number above 1200 milligrams. But in
2 the studies of Fumaderm, they report 720 milligrams,
3 referencing just how much dimethyl fumarate they were being
4 exposed to.

5 Q. You understand that Biogen criticizes the teasing out
6 of -- trying to tease out the active substance of DMF from
7 Fumaderm.

8 Do you understand that they try and make that argument?

9 A. Yes.

10 Q. Do you agree with that?

11 A. No.

12 Q. Why not?

13 A. So in multiple clinical trials that are relied upon by
14 Biogen even prior to the priority date, they recognize and cite
15 articles that support DMF as the active agent of Fumaderm.

16 So here in the context of litigation, while it seems
17 different, the record in the literature supports that it was
18 accepted, DMF being the active agent of Fumaderm.

19 Q. And if we could turn back to the Nieboer 1990 article,
20 which is JTX 2179. We looked at this, I think, first. Are you
21 aware that Biogen argues that Nieboer does not support that DMF
22 is the active component because Nieboer reports that, when you
23 consider the patients treated, the improvement percentage was
24 55 percent in the group treated with DMF compared with
25 80 percent in the Fumaderm group?

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1 A. Yes.

2 Q. And it's on page 5 of the article if you want to look at
3 it in your binder. We can call it up and turn to the
4 discussion section.

5 Do you agree with that criticism?

6 A. No.

7 Q. And why not?

8 A. So, while that reports the second sentence of the
9 paragraph, it leaves off the bottom of the paragraph where the
10 authors conclude "However, this difference was not significant,
11 and the final score in both groups was the same."

12 Q. I see. The last sentence in the paragraph.

13 A. Essentially saying that, when comparing in that trial, DMF
14 to Fumaderm, they were not seeing a significant difference
15 between the two.

16 Q. Okay. And now, if we can turn to discussing the
17 Th1-mediated diseases. We've been talking a lot about
18 psoriasis papers.

19 So why would a skilled artisan care about psoriasis
20 treatment, in your opinion, Dr. Greenberg?

21 A. So a skilled artisan in multiple sclerosis, while we start
22 off as neurologists, either by choice or by force, we rapidly
23 have to acquire the mindset of an immunologist because, at its
24 core, the autoimmune tenets of multiple sclerosis have been
25 shown for decades.

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1 And in that setting, we look to other conditions, other
2 autoimmune conditions, that share similar pathogenesis.

3 Q. And is that similar pathogenesis the Th1/Th2 shift you
4 described in the background of your testimony?

5 A. In the setting of multiple sclerosis and psoriasis, yes.

6 Q. Now, isn't it a little bit more complicated than just
7 herding cats?

8 A. Yes.

9 Q. For lack of a better pickup on your analogy.

10 Well, then, why would you really just focus in on this
11 shift, this imbalance, shifting imbalance in the immune system?

12 A. So, while multiple sclerosis and, frankly, all autoimmune
13 diseases are definitely more complicated than how we boil down
14 the simple explanations, we have a preponderance of evidence
15 that, in populations of patients, our simplified versions are
16 driving what they experience clinically.

17 And so while a Th1/Th2 imbalance would never explain all
18 MS in every patient, what we have found is that, when you have
19 therapies that shift the Th1/Th2 profile, patients get a
20 benefit. In fact, the earliest FDA-approved drugs for multiple
21 sclerosis that predate this agent significantly were studied
22 relative to just that notion, shifting the Th1 and Th2 immune
23 system balance and leading to a clinical benefit.

24 Q. If I didn't want to take your word for it, was there any
25 papers that were published in the literature that tied together

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1 the Th1/Th2 shifting with MS and psoriasis?

2 A. Yes.

3 Q. And let's look at JTX 2204, please.

4 And, again, this is the de Jong 1996 reference. Does the
5 de Jong 1996 reference disclose a tie between psoriasis and MS?

6 A. Yes.

7 Q. What does it disclose?

8 A. So de Jong, who was writing a paper entitled "Selective
9 Stimulation of T helper 2 Cytokine Responses by the
10 Antipsoriatic Agent Monomethyl Fumarate" -- so this is the
11 derivative, the metabolized form of DMF -- noted first that Th1
12 T cells and cytokines are thought to be involved in the
13 pathogenesis of psoriasis vulgaris and, when going further in
14 the paper, in discussion this notion of balance or imbalance in
15 autoimmune diseases, de Jong and colleagues noted that "An
16 immunopathologic role of polarized Th1 responses has been
17 proposed in organ-specific autoimmune diseases, like
18 experimental allergic encephalomyelitis (EAE)."

19 And EAE is the mouse model of multiple sclerosis. It is
20 the shorthand that will be used in literature to talk about the
21 immunology of multiple sclerosis.

22 Q. And so to close out, what does the de Jong 1996 article,
23 JTX 2204, teach a skilled artisan?

24 A. So de Jong and colleagues in '96 are supporting and in
25 peer-reviewed literature showing the acceptance that a

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1 prevailing theory of multiple sclerosis immunology, however
2 complicated we know it is in reality, was that the Th1/Th2
3 imbalance was playing a significant role in both of the
4 conditions, psoriasis and multiple sclerosis.

5 Q. Are there any other papers that you rely upon to support
6 this point?

7 A. Yes.

8 Q. And what is that?

9 A. So the next paper would be one from Morwitz in 2005.

10 Q. What does the Morwitz 2005 paper, which is JTX 2214, teach
11 the skilled artisan?

12 A. So Morwitz in 2005 noted, when looking at pathogenic
13 concepts of psoriasis, that, according to the T cell cytokine
14 expression profile, psoriasis is classified as a Th1-type
15 immune response.

16 They go on to say "Because several other inflammatory
17 diseases" -- and included in this is multiple sclerosis --
18 "follow similar immunological pathways of T cell activation,
19 psoriasis can be regarded as a visible disease model."

20 Q. What does that mean?

21 A. So, as referenced earlier today, this notion of
22 visible/invisible diseases, the authors here are laying
23 credence to and reinforcing the notion that immunologists take
24 relative to autoimmune diseases, that there are end organs that
25 are damaged, but what they share at an immunologic perspective

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1 is the same pathway of getting to that damage.

2 And what Morwitz is saying here is we have an opportunity
3 with psoriasis to have a visible disease model where you could
4 test theories about Th1-mediated disease because you can see a
5 rash come or go. You can look for clinical efficacy. It's
6 useful in the world of autoimmunity. And perhaps we could
7 apply this to some of the conditions that might be harder to do
8 clinical trials in.

9 They go on to say, beyond just linking multiple sclerosis
10 and psoriasis from an immunologic pathway perspective, to note
11 that fumaric acid, the mechanism of action of fumaric acid in
12 psoriasis might, therefore, be of interest in future use in the
13 treatment of diseases with a pathogenetic background similar to
14 this chronic skin disorder.

15 So Morwitz not only makes the connection immunologically
16 between psoriasis and MS, it makes the connection between
17 taking medications that were shown to be effective in psoriasis
18 and applying it to conditions like multiple sclerosis.

19 Q. And can we call up JTX 2221 and page 3, please.

20 What is Exhibit JTX 2221?

21 A. So 2221 is an abstract published by author Schimrigk and
22 colleagues entitled "An Open-Label, Prospective Study of Oral
23 Fumaric Acid Therapy for the Treatment of Relapsing-Relmitting
24 Multiple Sclerosis."

25 Q. And what does the Schimrigk 2004 article teach a skilled

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1 artisan?

2 A. So the Schimrigk 2004 article teaches an artisan that
3 dimethyl fumarate dosed to patients with multiple sclerosis
4 would achieve clinical success.

5 Q. And turning to the background, what does the skilled
6 artisan learn about the inflammatory processes between
7 psoriasis and MS?

8 A. So in the background they state fumaric acid is an
9 effective and safe therapy for psoriasis. And they go on to
10 say that, since the inflammatory processes involved in multiple
11 sclerosis are thought to be similar to those of psoriasis,
12 fumaric acid therapy may also be effective in treating MS.

13 Q. So this is the Schimrigk 2004 abstract. Did
14 Dr. Schimrigk, in fact, go on and explore the use of fumaric
15 acid in MS therapy in treating MS?

16 A. Yes.

17 Q. And so, as of the priority date, the hypothetical link
18 between MS and psoriasis and the Th1/Th2 shift was, in fact, a
19 reality, correct?

20 A. Correct.

21 Q. So skilled artisans had actually taken the leap and
22 started clinical trials with MS based on this -- what maybe
23 would have been a hypothesis in the 1990s; is that right? As
24 of the priority date?

25 A. So, while there were theories and animal studies and human

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1 studies showing the immunologic link and while there were
2 clinical trials showing the benefit of this drug in psoriasis,
3 what Schimrigk does is combine all of it and not just theorize
4 on it but act on it. Take the agent, apply it to patients with
5 multiple sclerosis in a clinical trial format, and measure over
6 time the clinical efficacy of the agent.

7 Q. Let's look at the Schimrigk study. And I think the first
8 one will be -- let's look at the poster, which is JTX 2222.

9 And, Dr. Greenberg, briefly, what is the Schimrigk 2004
10 poster, other than very small and hard to read?

11 A. So the 2004 poster was presented by Schimrigk and
12 colleagues in 2004 at a scientific meeting.

13 Q. And which scientific meeting was the poster presented?

14 A. So this would have been the American Academy of Neurology,
15 I believe. Let me make sure I'm referencing the right one.

16 Q. Actually, Dr. Greenberg, I think we'll get the answer to
17 that question when we go to the full abstract. But the poster
18 itself was presented at the meeting --

19 A. Excuse me. Go ahead. Sorry.

20 Q. That's okay. And the meeting was held in 2004?

21 A. Yes.

22 Q. What does the Schimrigk 2004 poster describe?

23 A. So it's entitled "A Prospective, Open-Label, Phase II
24 Study of Oral Fumarate Therapy for the Treatment of
25 Relapsing-Remitting Multiple Sclerosis," and it describes a

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1 clinical trial using fumarate therapy to treat multiple
2 sclerosis.

3 Q. If we could try and blow up the introduction in the upper
4 left-hand corner of the paper.

5 If you can read it, what does the third bullet point teach
6 the skilled artisan?

7 A. So the third bullet point of the introduction cites that
8 "Psoriasis is a chronic T-cell-mediated disease in which immune
9 suppressants have also been found to be effective and similar
10 to multiple sclerosis. A proinflammatory T helper 1, or Th1,
11 cytokine profile predominates in lymphocytes isolated from
12 psoriatic plaques."

13 Q. What does the next bullet teach the skilled artisan, if
14 anything?

15 A. The next bullet references literature specifically noting
16 that "Several open and double-blind clinical studies have shown
17 that oral fumarate therapy is effective in psoriasis."

18 Q. And has a citation 3 to 7.

19 Are any of those references familiar?

20 A. Yes. This includes the Kolbach reference, which we were
21 just discussing.

22 Q. The Kolbach 1992 reference?

23 A. Yes.

24 Q. And does the Schimrigk paper poster discuss the
25 involvement of the immune-mediated responses?

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1 A. It does. The last bullet of the introduction summarizes
2 the introduction, or makes the point within the introduction,
3 that "Given the involvement of immune mediated responses and
4 predominance of the Th1 cytokine profile in both psoriasis and
5 MS, the objective of this study was to determine if oral
6 fumarate therapy is effective in patients suffering from
7 relapsing-remitting multiple sclerosis."

8 Q. So the Schimrigk 2004 paper is reporting on an actual
9 clinical trial in patients suffering from MS?

10 A. Yes.

11 Q. And what were the -- actually, let's look at the design of
12 the trial, if we can. We can go back to the slides.

13 What was the design of the Schimrigk study?

14 A. So this was an open-label study that went on for over
15 70 weeks. It included -- it went on over 70 weeks. It
16 included a baseline phase of six weeks, during which patients
17 were followed but no treatment was offered.

18 And then they started the treatment phase of the trial,
19 which the first phase encompassed 18 weeks, during which they
20 were titrated up in their dosing of fumarate. And, as noted on
21 the slide, they started at a single pill and went up to six
22 pills of fumarate. And in the slide they reference this by how
23 much dimethyl fumarate the patient received at the end of that
24 titration, which was 720 milligrams of dimethyl fumarate.

25 Q. So if we can pause there. So the 720 milligrams above in

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1 the treatment phase is -- it's Fumaderm is being administered
2 in this study, correct?

3 A. It is. But what they're referencing is how much dimethyl
4 fumarate the patient ingested. If they were referencing the
5 number of milligrams of Fumaderm, it would be over
6 1200 milligrams.

7 Q. And it was -- the patients didn't start at 720 milligrams,
8 correct? They gradually moved up in dosage over that first
9 treatment phase of 18 weeks?

10 A. They did.

11 Q. And how long did it take them to titrate up to the
12 720 milligrams?

13 A. It takes approximately nine weeks to go up to the
14 720 milligrams.

15 Q. So in the first treatment phase, Fumaderm at
16 720 milligrams was given for approximately nine weeks?

17 A. Correct.

18 Q. And then what happens?

19 A. Then the medication was stopped, and they entered what was
20 called a washout period. So for four weeks, for a month,
21 patients were on no medication whatsoever. And then they
22 started back on a prolonged treatment phase for 42 weeks using
23 a titration up to a dose of only 360 milligrams a day of
24 dimethyl fumarate, again, dosed via the Fumaderm pill but
25 referencing just the amount of dimethyl fumarate the patients

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1 ingested.

2 Q. And approximately how long in the second treatment phase
3 did patients receive 360 milligrams of DMF?

4 A. So it was for at least nine months of that period of time.

5 Q. So the Slide X axis is a little truncated. The longest
6 phase, almost nine months of the 360 milligrams, was given over
7 an extended period of time?

8 A. Yes.

9 Q. And approximately how many patients were enrolled in the
10 study?

11 A. So this was a small study. It had ten patients enrolled.

12 Q. And how many completed the study?

13 A. Seven completed the study.

14 Q. And what was the primary outcome of the study?

15 A. So the primary outcome was to use the surrogate measure
16 that was mentioned earlier relative to multiple sclerosis,
17 specifically MRI metrics, to determine whether or not the dose
18 of medication that was being used would lead to a clinical
19 effect.

20 Q. And if we can turn to Figures 2 and 3 in the poster. And
21 what were the results of the study?

22 A. So shown on this slide, which is Slide 30, there are two
23 figures. The first figure is entitled "Figure 2. Change in
24 number of gadolinium-enhancing lesions." And it is a graph
25 showing the average number of lesions in the cohort of patients

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1 at baseline and then at the prespecified time points for
2 acquiring additional data, weeks 12, 18, 22, and then it goes
3 out to 46 and 70. And what it shows is there was a decline of
4 gadolinium-enhancing lesions through the course of the study
5 and a sustained reduction between weeks 22 and 70 of that
6 decline.

7 Q. And what was the dose administered during the sustained
8 reduction?

9 A. So for the majority of that time, patients were on
10 360 milligrams a day of dimethyl fumarate, dosed as Fumaderm.

11 Q. And you mentioned gadolinium-enhancing lesions. We're
12 going to talk about those a lot today.

13 What is a gadolinium-enhancing lesion?

14 A. So this is going to be an important concept today. So I
15 prepared just an example, if I can turn to it.

16 So this is Slide DDX 1100.31. And what I'm showing are
17 two images acquired by an MRI machine. And, if I can, I'll
18 just walk you through it.

19 Q. Sure.

20 A. So when you do an MRI scan, you're actually taking several
21 different pictures. So the reason people are on the machine
22 for up to an hour, bored out of their mind, is every five to
23 ten minutes we change the programming on the computer to
24 acquire the image in a different way.

25 So it's kind of like your iPhone. You can take a

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1 black-and-white photo or a color photo or a natural photo. We
2 can take a picture of the brain a lot of different ways because
3 we get different information from the different types of
4 pictures.

5 So on the left-hand side of this slide, what's entitled
6 "T2-weighted," anywhere that you see white is abnormal. It's
7 scar. This is a sequence we use to look at all the regions of
8 the brain that had previously suffered an insult from that
9 invading immune system that was chewing on the wires.

10 When I look at the T2-weighted image, I can't tell when
11 that scar formed. It could have been yesterday, last year, or
12 ten years earlier. There's no ability to date it. And that's
13 where the gadolinium-enhanced MRIs come in.

14 And what's shown on the right entitled "A T1-weighted
15 post-gad image" is the type of MRI we get after injecting
16 gadolinium into a person's veins. And what's supposed to
17 happen is the contrast stays in your blood system.

18 But if those pesky cats, if the immune cells are leaving
19 the blood supply and going into the brain, the gadolinium
20 follows them and highlights that area, and we know that that is
21 an actively inflamed lesion.

22 So when we talk about gad positive or Gd positive or
23 gadolinium-enhancing lesions, what we're referring to, as seen
24 here on this slide, that circle -- pointed out perfectly;
25 you're ready to be a radiologist -- that circle is where the

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1 gadolinium is accumulating and there's an active lesion going
2 on. So that gad MRI is there to look at how active a patient
3 is at that moment.

4 Q. Thank you. That's helpful. I have a feeling we're going
5 to talk a lot about gadolinium-enhancing lesions.

6 So what is the conclusion that is drawn -- or what does
7 the totality of the Schimrigk 2004 poster teach the skilled
8 artisan, in your opinion?

9 A. So the poster teaches several things. First, it indicates
10 that oral fumarate resulted in a significant improvement in
11 number and volume of gadolinium-enhancing lesions compared to
12 baseline. It looked at clinical measures both on function and
13 disease progression that were stable so things tracked
14 together. And they said the positive results of the study
15 suggest that larger trials should be undertaken to look at the
16 efficacy of oral fumarate in MS patients.

17 Beyond these conclusions, they validated and moved into
18 science what had been accepted, that both multiple sclerosis
19 and psoriasis were Th1-mediated diseases with a common
20 immunopathology and that, when using what was available to
21 them, which was Fumaderm, they did the dosing relative to how
22 much dimethyl fumarate the patient would be exposed to.

23 Q. Great. And is there also an abstract from the meeting
24 from the poster presentation?

25 A. There is.

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1 Q. Okay. If we could turn to JTX 2165, please.

2 And on the first page of the exhibit -- the first page, if
3 we could just stay there for a second -- where was the abstract
4 presented -- or where was the meeting?

5 A. This was at the 20th congress of what's called ECTRIMS,
6 which stands for the European Committee for Treatment and
7 Research in Multiple Sclerosis.

8 Q. Okay. And if we could look at the -- it's the next page
9 or the third page, please, page 4.

10 I believe on the bottom right --

11 If we could blow that up, please, bottom right.

12 Is this the beginning of the abstract?

13 A. It is.

14 Q. And it has a number under the title "Fumarate." What does
15 that say?

16 A. Yes. It's -- it projects poorly, but it's P642, which
17 correlates to the poster that we just discussed.

18 Q. And approximately how many people attend the ECTRIMS
19 meetings?

20 A. So ECTRIMS is one of the largest MS-dedicated
21 international meetings in the world. And it receives usually
22 thousands of individuals, both clinicians and scientists, who
23 are either doing MS clinical work, clinical trials, or basic
24 science.

25 Q. And so the poster was available at the meeting. And what

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1 does the abstract, which is JTX 2165, teach the skilled artisan
2 about the Schimrigk study?

3 A. So the abstract notes in the background that oral fumarate
4 was effective and safe for the treatment of psoriasis. And it
5 says "Similar to psoriasis, the inflammatory process in
6 multiple sclerosis is thought to be mediated by a Th1-type
7 cytokine reaction due to global immune suppression or a
8 Th2-mediated bistandard suppression."

9 Q. And looking down a couple lines, the dose that was
10 administered of Fumaderm is also reported in terms of the DMF
11 active amount provided?

12 A. Yes.

13 So when they indicate that all patients were treated with
14 oral fumarate therapy -- and what they had access to and they
15 noted in the abstract was Fumaderm -- that they were titrated
16 to a maximum of six tablets per day. And in the parentheses
17 the milligram dose they note is not the milligrams of Fumaderm;
18 it's the milligrams of dimethyl fumarate.

19 And then in the second treatment period, when they note
20 that patients were on three tablets a day of Fumaderm, again,
21 in the parentheses, the 360 milligrams that the authors note
22 only refer to how much dimethyl fumarate patients were being
23 exposed to.

24 Q. And how often were the doses administered in the study?
25 What was the frequency of the dosing?

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1 A. And so when they were doing this trial, patients were
2 getting equal doses three times a day.

3 Q. And if we can look at Slide 33.

4 What were the conclusions of the Schimrigk 2004 abstract?

5 A. So in the abstract, they note that there were significant
6 reductions from baseline in the number of gadolinium-positive
7 lesions were observed starting after week 12 of treatment with
8 fumarate. And they associate a P value of less than 0.05 and
9 go on to say "In addition, there were significant reductions
10 from baseline in gad-positive lesion volume starting after week
11 12." And again they give a P value there of less than 0.01.

12 Q. What's the -- what is a P value?

13 A. A P value is a reporting that a statistical test has been
14 applied to the data to determine whether or not the results
15 were observed due to chance alone or whether or not they were
16 likely due to the intervention that was being studied.

17 And when you have a P value of less than .05, it's usually
18 considered to be statistically significant that the outcome
19 that was observed was not due to chance alone.

20 Q. And so what does the abstract teach the skilled artisan
21 about the effectiveness of the 360-milligram dose of DMF?

22 A. So in the conclusions, they note that oral fumarate
23 therapy significantly reduced both the number and volume of
24 gad-positive lesions over 70 weeks of treatment.

25 So this was a trial that went on for well over a year.

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1 And for most of the time when being treated, patients were
2 being dosed with 360 milligrams a day. And in a statistically
3 significant way, patients were achieving a radiographic
4 remission. The medication was preventing those confused cats
5 from getting into the brain and causing those
6 gadolinium-enhancing lesions.

7 Q. Did Schimrigk encourage others to continue looking for
8 treatments for MS?

9 A. Schimrigk and colleagues ended the conclusion by stating,
10 "These findings indicate that oral fumarates may be a promising
11 new treatment for relapsing-remitting multiple sclerosis."

12 Q. Would a skilled artisan looking at the Schimrigk 2004
13 study think that the maintenance dose of the 360 milligrams
14 given over nine or ten months would be attributed to the
15 720-milligram amounts given earlier in the study for nine
16 weeks?

17 A. I'm sorry, ma'am. Can you repeat that.

18 Q. Would a skilled artisan attribute the effect of the DMF in
19 the 360-milligram arm to the nine-week earlier treatment of
20 720 milligrams?

21 A. No.

22 Q. And why not?

23 A. So the amount of time that patients were on the
24 720-milligram while in the initial phase was relatively short,
25 followed by a washout period during which patients were on no

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1 medication, allowing immune systems to start shifting again, if
2 you were. But then they were maintained on 360 milligrams for
3 the majority of time during the study. And what we didn't see
4 was a rebound of inflammation.

5 When looking at the baseline scans of these patients, they
6 had a lot of activity. These were not patients with one or two
7 lesions; they had multiple lesions enhancing at the beginning.
8 And yet they were able to maintain a remission for a long
9 period of time with 360 milligrams of dimethyl fumarate.

10 Q. And because Fumaderm was administered in the study, would
11 it motivate a skilled artisan to dose higher than
12 720 milligrams?

13 A. No.

14 Q. Why not?

15 A. So there's several reasons.

16 First off is efficacy had been achieved in a statistically
17 significant way with this dose range of 360 and not going
18 higher than 720.

19 And when we think about autoimmune diseases, we are
20 looking to achieve success, shift the immune system, and then
21 stop exploring higher doses, because there are a lot of
22 reasons -- side effects, concerns about the unknown -- that
23 would push us away from going higher than 720.

24 At this time -- and we'll get to it in the literature --
25 the Fumaderm label itself expressly spoke against going beyond

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1 720. And Schimrigk's practice clearly identified 360 to 720 as
2 an effective intervention for multiple sclerosis patients.

3 Q. Does the fact that only a small number of patients
4 finished the study influence your opinion on whether skilled
5 artisans would rely on the conclusions of Schimrigk?

6 A. No. I think skilled artisans looking at the literature,
7 when trying to find therapies, are hoping to have a reasonable
8 expectation of success.

9 We're not a regulatory agency. So I am not proclaiming
10 that an FDA would approve dimethyl fumarate based on a
11 ten-person trial. But a skilled artisan looking for therapies
12 would look at this study that was over a long period of time
13 with the gold standard of a surrogate measure of activity,
14 specifically, the MRI, and following these patients and showing
15 that prolonged response, that there would be -- that reasonable
16 expectation that dosage in this range would work for MS.

17 Q. Are you aware that Biogen's experts criticize the
18 Schimrigk study because it's not placebo-controlled?

19 A. Yes.

20 Q. Do you agree with that criticism?

21 A. No.

22 Q. Why not?

23 A. For the purposes of obviousness, again -- and not a
24 regulatory agency -- we're looking to see if it was a
25 well-executed and well-designed study. The point of a control

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1 is there to determine statistical significance for the FDA to
2 approve, for the EMA to approve. But when looking for
3 different options to treat our patients, a trial like this
4 would speak to a skilled artisan.

5 We've got patients who respond to different agents. And
6 as we find ones that have a reasonable expectation of success,
7 we would pursue it.

8 Q. Does the concept of regression to mean apply in the
9 context of the Schimrigk study?

10 A. So in the past there's been question relative to the
11 Schimrigk study on the notion of regression to the mean. And
12 it's important to recognize what that is and how it doesn't
13 apply.

14 So regression to the mean was the statistical issue in
15 multiple sclerosis that really prompted the need for
16 placebo-controlled trials for regulatory agencies to determine
17 the relative efficacy of a given intervention. And the issue
18 was rooted in clinical events, not MRI events.

19 So if I enrolled 10, 100, 1,000 patients who had all had
20 multiple relapses in the preceding year into a trial and over
21 the next year, with no control, saw the number of relapses
22 decline, the concern would be that it happened due to
23 regression to the mean, that they had an active year followed
24 by an inactive year, and I would inappropriately ascribe their
25 inactive year to my therapeutic intervention.

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1 And it has to do with how relapses get defined and how we
2 track relapses when somebody is enrolled in a trial.

3 For an MRI outcome, where you get a baseline scan, where
4 you quantify how active they are, we don't see the same
5 phenomenon of regression to the mean over the course of a year
6 or more as seen in the Schimrigk study.

7 Q. And that's because you actually understand the starting
8 point of the patient's disease state?

9 A. We're not taking a historical record of what happened over
10 the prior years. We're not asking how many relapses or
11 inferring. We have a baseline measure that we can follow over
12 time.

13 Q. And there's another Schimrigk abstract we can look at, and
14 that's Schimrigk 2005.

15 If we could look at JTX 2221, or Slide 34.

16 Is this another abstract of the same Schimrigk study?

17 A. Yes.

18 Q. And, again, Schimrigk is again reporting the results of
19 his study in 2005 at this time; is that correct?

20 A. Correct. This happened in April of 2005 at the American
21 Academy of Neurology.

22 Q. And it also reports on the favorable results of the study?

23 A. It does.

24 Q. And if we could look at the Schimrigk 2006 paper.

25 And before we get there, so was the Schimrigk study

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1 repeated in the art numerous times?

2 A. Yes.

3 Q. Approximately how many times does Schimrigk's study get
4 reported?

5 A. At least three or four.

6 Q. But they're all the same study?

7 A. It appears to be so.

8 Q. Now, looking at the Schimrigk 2006 paper, which I just
9 want to briefly look at. And it's at the bottom of page 5 to
10 the top of page 6.

11 Are you aware that Biogen's experts rely on the Schimrigk
12 2006 paper to say -- to criticize the design of the Schimrigk
13 study because it was baseline-controlled and therefore there
14 was a possibility that patients have high disease activity?

15 A. Yes.

16 Q. And I think -- and where do they draw that criticism from
17 in the 2006 paper?

18 A. So the criticism is around whether or not having a
19 baseline period would be adequate to control in a small study
20 for the enrolled patients and their course over time. And so
21 the concern is whether or not it would impact conclusions that
22 are being drawn about the study.

23 Q. And do you share that concern?

24 A. I do not.

25 Q. And why not?

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1 A. So as we see highlighted here, the authors call this out
2 even in the publication. And they say, "Given the
3 baseline-controlled nature of this study, the possibility that
4 patients were recruited during a period of high disease
5 activity must be considered."

6 But they go on to say, "A six-week baseline period was
7 included to control for this possibility."

8 So they were essentially recognizing that, if you didn't
9 have a baseline period, if you just enrolled people on day one,
10 you could get people who were about to have a relapse or about
11 to go a certain way in terms of their condition. So they
12 specifically brought people in and said, "Don't take any
13 medicine for six weeks" to level the playing field and ensure
14 they weren't enrolling someone who would be uniquely different
15 from the rest of the population.

16 Q. And so setting aside the Schimrigk 2006 paper which Biogen
17 is relying upon, up until this point in time -- I think we're
18 up to about approximately 2004, 2005 -- what does a skilled
19 artisan know about using DMF in the treatment -- in the
20 clinical setting of patients with MS?

21 A. So a skilled artisan knows several things.

22 First, that there had been an actual clinical trial of
23 this agent in patients with multiple sclerosis that achieved a
24 statistically significant outcome of success. So the drug was
25 there, it was efficacious, and the dose range that was used was

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1 360 to 720, with the majority of time being on 360 milligrams a
2 day.

3 And they were also firm in the knowledge that what had
4 been a theory in terms of multiple sclerosis and psoriasis
5 sharing a similar immunopathology had borne out, because the
6 success that was experienced in multiple sclerosis had already
7 been experienced in psoriasis in multiple large-scale,
8 long-term studies. And in those studies, a dose of
9 480 milligrams had been shown to be effective in patients with
10 the autoimmune disease psoriasis.

11 Q. And did the art then move into using DMF as a monotherapy
12 in the clinical setting to treat patients with MS?

13 A. Yes.

14 Q. And if we could look at the DTX 1104.

15 And another poster. And I'm hoping we can blow it up at
16 periods of time.

17 What is the DTX 1104?

18 A. So this is a poster by colleagues listed there. The first
19 author is Ludwig Kappos. The last author is Rebecca Conaghan.
20 And it's entitled "A Randomized Placebo-Controlled Phase 2
21 Trial of a Novel Oral Fumarate, BG00012, in Patients With
22 Relapsing-Remitting Multiple Sclerosis."

23 Q. And where was this poster presented?

24 A. So this is a poster that was presented at the 15th meeting
25 of the European Neurological Society.

1 Q. And when was it presented?

2 A. In June of 2005.

3 Q. And throughout your testimony today, you'll be referring
4 to Biogen's Phase 2 study using DMF to treat MS as "the Kappos
5 Phase 2 study."

6 Do you understand that?

7 A. Yes.

8 Q. Okay. Who sponsored the study presented in the Kappos
9 2005 poster?

10 A. So this was sponsored by Biogen Idec and Fumapharm AG.

11 Q. And does the Kappos 2005 poster also refer to the
12 psoriasis studies?

13 A. It does.

14 Q. In what way?

15 A. So in the introduction right at the beginning of the
16 poster on the top left, the second bullet point states "Fumaric
17 acid esters have been used in Germany for the treatment of
18 psoriasis. The efficacy of fumaric acid esters in psoriasis is
19 thought to be mediated in part by their immunomodulatory
20 activity, suggesting that these agents may also be effective in
21 multiple sclerosis."

22 They go on to cite the Schimrigk study that we've been
23 referencing, noting that "In an open-label pilot study of ten
24 patients with multiple sclerosis, the fumaric acid ester
25 therapy reduced the number and volume of gadolinium lesions on

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1 T1-weighted magnetic resonance imaging scans of the brain."

2 Q. And in this poster does it disclose that the active
3 ingredient administered is BG-12, or dimethyl fumarate?

4 A. It does. In Figure 1 of the poster, it has a molecular
5 structure of BG-12, and then the name is dimethyl fumarate.

6 Q. And what was the design of the Kappos Phase 2 study?

7 A. So in Figure 2, there's an outline of the design which is
8 a multiarm trial. The study began with a screening phase,
9 usually to make sure patients meet the inclusion-exclusion
10 criteria as set out by the trial design. And then they enter
11 the randomization phase before starting one of their, in this
12 case, four different treatment arms.

13 Q. And how much of DMF was administered in each of the
14 treatment arms?

15 A. So one of the arms received a placebo, and the other three
16 arms received either 120 milligrams a day, 360 milligrams a
17 day, or 720 milligrams a day.

18 Q. And, again, this is actually of DMF itself, not the active
19 component of Fumaderm?

20 A. This is dimethyl fumarate.

21 Q. And this is in 2005?

22 A. Yes.

23 Q. So what does the Kappos -- I'm sorry.

24 What was the primary end point of the study?

25 A. So the primary end point of the study, as is typical in

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1 Phase 2 multiple sclerosis trials, was to use MRI outcomes, the
2 gadolinium-enhancing lesions, just as was done by Schimrigk and
3 colleagues.

4 Q. And so what does, in your opinion, the Kappos 2005 poster
5 teach the skilled artisan?

6 A. So the Kappos 2005 poster acknowledges the literature
7 that's accessible in the art that multiple sclerosis and
8 psoriasis share a common immunopathogenesis; that fumarates,
9 which have been successful in treating psoriasis, were also
10 known to be successful for treating multiple sclerosis by
11 citing the Schimrigk study.

12 They go on to indicate that BG-12 is dimethyl fumarate
13 such that in the future, when reading literature about BG-12,
14 skilled artisans would know it was referring to DMF.

15 Q. And there's no confusion about what is the active
16 component in the Kappos study that's being used?

17 A. None. They specifically use the dose range of 120 to
18 720 milligrams of just dimethyl fumarate as a monotherapy, not
19 dosed as Fumaderm or anything else.

20 Q. Did the skilled artisan have any additional information
21 about the Kappos Phase 2 study in 2005?

22 A. So in 2005, the skilled artisan would know that this dose
23 range was being used and that DMF was the active ingredient in
24 BG-12, coming from an announcement of the trial in a online
25 archive called ClinicalTrials.gov.

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1 Q. And turning to ClinicalTrials.gov, that's DTX 1135.

2 And turning to the top, what is the title of the trial?

3 A. So the title of the trial, the official title is
4 "Double-Blind Placebo-Controlled Dose-Ranging Study to
5 Determine the Efficacy and Safety of BG-12 in Subjects with
6 Relapsing-Remitting Multiple Sclerosis."

7 Q. And does the ClinicalTrials identify what BG-12 is?

8 A. It does. The very first portion of a sentence in the
9 brief summary is "DMF, the active ingredient in BG-12, is an
10 immunomodulator demonstrating definite therapeutic efficacy in
11 psoriasis and possible therapeutic efficacy in multiple
12 sclerosis."

13 Q. And does the ClinicalTrials provide the dosing regimen for
14 the Kappos Phase 2 study?

15 A. It does.

16 Q. And what was it?

17 A. In the detailed description, they outline the four arms as
18 previously mentioned: the 120 milligrams a day,
19 360 milligrams a day, 720 milligrams a day, and a placebo arm.

20 Q. And does the trial -- the ClinicalTrials document provide
21 any instructions to clinicians relating to dose reduction?

22 A. It does.

23 Q. Can you look at that on page 2 of DTX 1135, please.

24 A. And so, as shown on the slide here, which is Slide 38,
25 they indicate that "dose reduction will be allowed for subjects

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1 who are unable to tolerate investigational drug."

2 Q. What does that mean to a skilled artisan?

3 A. So it recognizes -- it's affirming what's been seen in the
4 field of psoriasis and multiple sclerosis and all of the
5 fumarate literature, that there are dose-limiting side effects.
6 And clinicians needed to be aware and be prepared to adjust the
7 dose of a patient if they were having difficulty tolerating it.

8 So instead of just removing a patient from the study, they
9 were allowed to adjust down.

10 Q. And is the ClinicalTrials information something that
11 skilled artisans typically would consult and rely upon?

12 A. Yes.

13 Q. And was there another BG-12 or DMF study by Kappos?

14 A. Yes.

15 Q. Is that DTX 1102?

16 A. Yes.

17 Q. Okay. And what is DTX 1102, also titled the Kappos 2005
18 abstract?

19 A. So this is an abstract in the Journal of Neurology in
20 2005, the supplement. And it's entitled "A Randomized
21 Placebo-Controlled Phase 2 Trial of a Novel Oral Single-Agent
22 Fumarate Therapy, BG-12, in Patients with Relapsing-Remitting
23 Multiple Sclerosis."

24 Q. And what does the Kappos 2005 abstract describe?

25 A. So the background indicates that it's describing the

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1 open-label pilot study -- it described "An open-label pilot
2 study demonstrated that a product containing a mixture of
3 fumaric acid esters significantly reduced the number and volume
4 of gad-enhancing lesions in patients with relapsing-remitting
5 multiple sclerosis. BG-12 is being investigated for the
6 treatment of psoriasis and other autoimmune diseases, including
7 multiple sclerosis."

8 Q. And do you know what study it's referencing in the
9 background, which clinical trial?

10 A. This would be the Schimrigk study.

11 Q. And what doses were patients administered in the Kappos
12 Phase 2 study?

13 A. So in the Phase 2 study, as seen, I believe, on the next
14 slide, which was Slide 40, it outlines the 120-milligram-a-day,
15 360-milligram-a-day, 720-milligram-a-day, and placebo arm of
16 the trial.

17 Q. And how is this study characterized?

18 A. So this study is characterized as a dose-ranging study.

19 Q. And what is a dose-ranging study?

20 A. So it's not unusual, when we have agents that we have a
21 reasonable expectation of success will work for a patient, that
22 we are looking to find the dose that makes the most sense. And
23 we're balancing the issues of efficacy, tolerability, patient
24 convenience, and compliance.

25 And so when we do studies, we'll do a dose-ranging study

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1 to gather data about this and make an assessment.

2 Q. And so what does the abstract teach a skilled artisan
3 about the Kappos study?

4 A. So the skilled artisan knows that there's recognition of a
5 successful study of fumarates in multiple sclerosis, there's a
6 recognition that multiple sclerosis and psoriasis are
7 immunopathogenically similar conditions, and that fumarates
8 have worked for psoriasis. And there's a recognition that,
9 looking at doses in this range -- in this study it was 120 to
10 360 milligrams a day -- were being evaluated to look for
11 efficacy, tolerability, and safety.

12 Q. Now, as of the end of 2005, do we have any results from
13 the Kappos Phase 2 study?

14 A. So at the end of 2005, it's over. But the first release
15 comes the next year.

16 Q. And let's look at the January 2006 press release, which is
17 DTX 1136.

18 What is being announced here?

19 A. So this is a press release from January 9th, 2006, in
20 Business Wire. And it reads, "Biogen Idec and Fumapharm AG
21 today announced that a Phase 2 study designed to evaluate the
22 efficacy and safety of BG-12, an oral fumarate, in patients
23 with relapsing-remitting multiple sclerosis met its primary end
24 point."

25 Q. And did the skilled artisans understand what BG-12 is by

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1 January 2006?

2 A. Yes.

3 Q. And does the skilled artisan understand, by January 2006,
4 which doses were used in the study?

5 A. Yes. That had been disclosed in both the
6 ClinicalTrials.gov, the abstract, and the poster.

7 Q. And, in your opinion, would a skilled artisan reading the
8 press release in January 2006 know which dose was effective in
9 treating multiple sclerosis?

10 A. So looking at this, a skilled artisan would know that at
11 least the 720-milligram dose had been effective.

12 Q. And so as of January 2006, what did the prior art teach a
13 skilled artisan?

14 A. So as of January 2006, a skilled artisan would know, in a
15 large Phase 2 trial, that at least 720 milligrams of dimethyl
16 fumarate as a monotherapy was effective relative to multiple
17 sclerosis.

18 They would know that, in multiple sclerosis, a trial over
19 70 weeks had shown dose ranges between 360 and 720 to have a
20 clinical effect.

21 They would know that multiple sclerosis and psoriasis were
22 immunologically kindred spirits with a shared pathway, albeit
23 different end organs getting damaged.

24 And they would know, in psoriasis, that the field had
25 coalesced around dimethyl fumarate being the active component

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1 of Fumaderm. And when dosed with 480 milligrams a day of
2 dimethyl fumarate, psoriasis patients were able to achieve an
3 immunologic and clinical remission.

4 Q. And so, as of this time, it's January 2006, and all of the
5 art we've considered up until this point in time is before
6 then; is that correct?

7 A. That's correct.

8 MS. BLOODWORTH: And, Your Honor, this is a good time
9 for a break, if that's a good time.

10 THE COURT: Again, I will see what's happened to our
11 climate control in here, if I can't get that somewhere north of
12 the equator. Thank you.

13 Thank you, Doctor. You remain on direct examination
14 and should return to the stand at 10 after 3:00.

15 Wait a minute. Was that enough time for everybody to
16 use the facilities, or do you need another five minutes?

17 MS. BLOODWORTH: Maybe 3:15, Your Honor?

18 THE COURT: 3:15 is fine. Thank you.

19 (Recess taken. 2:56 to 3:16.)

20 THE COURT: Let me give you a weather report.

21 Thanks to our deputy clerk, Sheree Burlas, things are
22 being checked on. If you're not here tomorrow, if this does
23 not change this afternoon, there's going to be a service call
24 placed and someone will be in here tomorrow to take care of it.
25 Everything was fine yesterday. So nobody knows what happened

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1 other than the weather changed and, apparently, the system
2 doesn't like it. I don't know. It's hard for me to say. But
3 we'll -- if you could bear with us today, we'll -- we hope to
4 have it improved, if not completely fixed, by Thursday.

5 And also, just for purposes of scheduling, would you
6 all be able to and willing to start, say, at 8:30 from now on,
7 since we've been through the first day? Or, if it's a problem,
8 9:00?

9 MR. FELDSTEIN: 8:30 is fine, Your Honor.

10 MS. BLOODWORTH: It's fine.

11 THE COURT: That's great. I think then we'll be sure
12 to get through all this.

13 MS. BLOODWORTH: Two housekeeping matters for the
14 testimony we just went over, Your Honor. First, I failed to
15 officially offer Dr. Greenberg as an expert. So if I may do
16 so. Maybe a little late than never.

17 THE COURT: There hadn't been any objection yet. So
18 I figured that it was a given. But go ahead. In what areas?

19 MS. BLOODWORTH: I'd like to move -- Mylan offers
20 Dr. Greenberg as an expert with a medical degree and at least
21 three years of training in neurology and at least three years
22 of clinical experience treating multiple sclerosis. So we'd
23 like to move him as an expert in neurology and multiple
24 sclerosis treatment.

25 THE COURT: Is there any objection?

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1 MR. FELDSTEIN: No objection, Your Honor.

2 THE COURT: Dr. Greenberg -- the Court accepts
3 Dr. Greenberg as an expert in the areas of neurology and
4 multiple sclerosis treatment and qualified to offer opinions in
5 those areas.

6 You may proceed.

7 MS. BLOODWORTH: Your Honor, one more housekeeping
8 matter. I think I was referring to the Kappos 2005 abstract,
9 and I'm told I forgot to mention the exhibit number. And so,
10 just in case, the Kappos 2005 abstract is DTX 1102. And so
11 that's the exhibit that testimony right before the break was
12 relating to.

13 THE COURT: I'm forgetting which one we were on, but
14 I think I circled it. I saw it. Thank you.

15 MS. BLOODWORTH: Thank you, Your Honor.

16 BY MS. BLOODWORTH:

17 Q. Now, Dr. Greenberg, up until the break, all of the art
18 that we had been focusing on is as of January 2006 or earlier,
19 correct?

20 A. Correct.

21 Q. So now I'd like to transition into the next part of the
22 testimony, which is the skilled artisans, whether or not they'd
23 have a motivation or reasonable expectation of success.

24 Did you provide or prepare a demonstrative to discuss
25 motivation?

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1 A. I did.

2 Q. And if we could turn to Slide 42, please.

3 A. So on Slide 42 it shows the different pieces of data and
4 information and considerations that a person skilled in the art
5 would take into consideration when being motivated to use a
6 dose of 480 milligrams. And if you start on the outside of the
7 bull's-eye, kind of the guardrails around dosing, we know that
8 doses less than -- 720 milligrams and less have been used
9 effectively to treat multiple sclerosis. And we know this from
10 Kappos, and we know this from Schimrigk. And, while we have
11 evidence in psoriasis of a large dose range, even in MS alone
12 we know that 720 works.

13 But you're motivated to look for a regimen that reduces
14 side effects. And in the world of fumarates, there have been
15 concerns mentioned of dose-dependent side effects. And you
16 also want to optimize a dose, and that optimization means
17 balancing -- finding a dose that is going to shift the immune
18 system away from that Th1 to a Th2, as evidenced either by
19 basic science or clinical trials, and optimize a dose that
20 would highlight patient compliance.

21 And it's always hard for us to remember to take multiple
22 pills a day, multiple times a day. So when looking at
23 different dosing regimens, if you can reduce from four to three
24 or ideally three to two or less times a day, you increase
25 compliance among patients.

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1 So in a world where we have access to pills that come in
2 120 milligram increments and we want to pick a dose in this
3 360-to-720 range and highlight something that's equal doses
4 twice a day, it would motivate us to target 480-milligrams a
5 day.

6 Q. Thank you.

7 Did you also have a brief summary slide of the points of
8 motivation you just mentioned?

9 A. I did. Just on the off-chance that I did a very bad job
10 of explaining my thoughts, there were the bullets that we
11 wanted to reduce side effects, optimized within the range that
12 we know is effective. We had the trail of 360 to 720 already.
13 So we were within that range.

14 We wanted to optimize compliance, which motivates us to do
15 twice-a-day dosing, and the math was utilizing 120-milligram
16 increments. And so the dose that fits all of those motivating
17 features is a dose of 240 milligrams twice a day, equaling a
18 total daily dose of 480 milligrams.

19 Q. And so turning first to reducing side effects, there's --
20 you're aware, of course -- and, actually, if we can go back to
21 the bull's-eye slide on Slide 42, I notice there's a less-than
22 sign in front of the 720.

23 A. Yes.

24 Q. And is it your opinion that a skilled artisan would not --
25 would not want to dose higher than 720?

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1 A. Correct.

2 Q. And why not, briefly?

3 A. So several reasons. First off, there's already data
4 showing efficacy at 360 to 720. So just from an immunologic
5 point of view, we have a target within that range. But beyond
6 that, there are a couple express warnings in the literature
7 relative to going the higher doses. And they relate to the
8 possibility of side effects at doses as you go up and
9 specifically as you go above 720.

10 Q. And so if we could look at the Fumaderm label, which is
11 JTX 2158 and page 2. Are you familiar with the Fumaderm label,
12 Dr. Greenberg?

13 A. Yes.

14 Q. And what is the Fumaderm label?

15 A. So this is the summary of product characteristics that's
16 marketed as Fumaderm and approved in Germany for psoriasis. It
17 names the medicinal product and the composition of that
18 product.

19 Q. And if we can look at page 8, when was it dated?

20 A. So the date of revision of the text is April 2005.

21 Q. When was its first authorization?

22 A. The first authorization is in 1994.

23 Q. And what does the Fumaderm label say about side effects?

24 Again if you look at page 5.

25 A. So on page 5 it lists the undesirable effects, the side

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1 effects. And amongst them it lists facial redness or hot
2 flushes, referring to the experience patients have after
3 swallowing a pill, they feel flushed and hot and uncomfortable;
4 the gastrointestinal disorders, including diarrhea; and
5 abdominal cramps or flatulence; among others.

6 Q. Why are these type of GI side effects a concern for a
7 skilled artisan?

8 A. So, first, we don't like to torture our patients with side
9 effects. So just from a general humanity perspective, we try
10 to be kind about things.

11 But we also have to recognize that, when we are
12 recommending and prescribing medications for patients, that
13 it's always a decision from the patient on taking the medicine
14 as prescribed and being compliant. And the more side effects
15 go up, naturally, people tend to miss doses or avoid the
16 medication.

17 And so, when we're talking about chronic diseases like
18 multiple sclerosis, for example, where a lot of our patients
19 aren't having any symptoms, they're in between attacks and they
20 feel well, to experience side effects from a medication would
21 definitely have an impact on their quality of life and on
22 whether or not they'd be compliant with the medication.

23 Q. Does the Fumaderm label contain a warning to physicians
24 about how much to prescribe to patients?

25 A. It does.

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1 Q. And what is that warning?

2 A. So it expressly states, after going through the titration
3 schedule of Fumaderm, that the maximum daily dosage of 3 by 2
4 gastroresistant Fumaderm tablets must not be exceeded. And the
5 3 by 2 is referring to 240 milligrams three times a day or a
6 dose of 720 milligrams of DMF in a day.

7 Q. So what does the Fumaderm label teach a skilled artisan?

8 A. So the Fumaderm label both explains what the expected side
9 effects would be, discusses the fact that there is a dose
10 dependence to the side effects, and gives a clear warning -- in
11 fact, uses the term "must not exceed" that upper range of
12 dosing, which would include -- which would be at the
13 720 milligram dose of dimethyl fumarate.

14 Q. Have side effects always been associated with DMF?

15 A. To my knowledge, in each of the papers I have read talking
16 about this agent relative to humans, they reference side
17 effects.

18 Q. And if we could look at the JTX 2168, turning to page 4.

19 What is Exhibit 2168? Maybe we can call up the title,
20 please, and the authors.

21 A. So the title of this is "Fumaric Acid Therapy for
22 Psoriasis: A Randomized Double-Blind Placebo-Controlled
23 Study." The first author is Nugteren-Huying. This was
24 published in 1990.

25 Q. And what doses of DMF treatments were administered? And

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1 this is to psoriasis patients, correct?

2 A. This is to psoriasis patients. And there were groups of
3 patients. But when looking at the enteric-coated tablets, the
4 Fumaderm, which includes the 120 milligrams of dimethyl
5 fumarate, Group 1 was given those tablets. And then,
6 ultimately, the dosage schedule called for a gradual increase
7 from one to six tablets daily, so getting to that upper range
8 that's referenced in the Fumaderm label.

9 Q. And, again, we've discussed how skilled artisans
10 understood Fumaderm to be the equivalent of dimethyl fumarate.
11 What did the article JTX 2168 report about the efficacy of
12 the treatment on psoriasis?

13 A. So in the discussion they noted that the results of the
14 study show that oral treatment with tablets containing a
15 combination of dimethyl fumarate and monoethyl fumarate may be
16 effective in the treatment of psoriasis.

17 Q. Did the article talk about the side effects?

18 A. It does.

19 Q. What did it say about that?

20 A. It confirms what we see in the label and other literature,
21 specifically the main side effects of the treatment in the
22 group that received active therapy, Group 1, were flushing,
23 diarrhea, fatigue, and nausea.

24 Q. And were the side effects also mentioned in the discussion
25 of the paper?

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1 A. Yes.

2 Q. And what did the author discuss about the side effects?

3 A. They indicated that the drawback of fumaric acid therapy
4 may be its side effects.

5 Q. And so what does JTX 2168 teach the skilled artisan, in
6 your opinion?

7 A. So, when looking at the dosing regimens, it's teaching
8 that, as you get to the 720 milligram equivalent dose of DMF,
9 in this case it was as Fumaderm, you see that there are
10 dose-limiting side effects. And they specifically call out
11 that you should look at regimens that would minimize these
12 problems.

13 Q. And did these side effects, they reported repeatedly
14 throughout time in your opinion?

15 A. In my opinion, based on the literature I've read,
16 consistently, these side effects are recognized and reported in
17 clinical trials.

18 Q. So let's move forward about 15 years to 2005 and look at
19 the Biogen press release, DTX 1133. We can call up the top
20 part.

21 What is DTX 1133?

22 A. So DTX 1133 is a press release in BusinessWire from
23 April 7th, 2005, and it was released by Biogen Idec and
24 Fumapharm AG, the title of which is "BG-12 Psoriasis Study
25 Meets Primary Endpoint; Oral Compound Also Being Studied for MS

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1 in Phase II Trial."

2 Q. So a skilled artisan understands in 2005 that BG-12 is
3 dimethyl fumarate?

4 A. Yes.

5 Q. And this is a study in psoriasis, using BG-12?

6 A. Correct.

7 Q. And what does the press release say about the Phase 3
8 trial design?

9 A. So the trial was a multicenter double-blind
10 placebo-controlled Phase 3 study of 175 patients who had
11 moderate to severe psoriasis, and they were randomized to
12 receive either placebo or 720 milligrams of BG-12 a day for
13 16 weeks. And then they were followed relative to an outcome
14 measure specific for psoriasis.

15 Q. Did the press release report on the side effects at all of
16 the study?

17 A. It did.

18 Q. And what did it say about that?

19 A. In the study the most commonly reported adverse events
20 were flushing and diarrhea. In addition, one patient was
21 hospitalized for pneumonia, and one patient was hospitalized
22 for kidney stones.

23 Q. Is this consistent with your understanding of the side
24 effects of Fumaderm?

25 A. Yes.

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1 Q. And is it consistent today with the administration of
2 Tecfidera?

3 A. To my understanding, yes.

4 Q. And so what does -- so let's look at another reference.
5 Let's look at DTX 1001, which I think is the Joshi patent we
6 talked about earlier already.

7 Did you rely upon the Joshi patent for any teaching
8 relating to the side effects of DMF?

9 A. Yes.

10 Q. And what does the Joshi '999 patent say about side
11 effects?

12 We can go to page 6 at Column 5, please, about lines 28.

13 A. So the Joshi patent notes that "By administration of the
14 diethyl fumarates in the form of microtablets, which is
15 preferred, gastrointestinal irritations and side effects, which
16 are reduced already when conventional tablets are administered,
17 but is still observed."

18 Q. And is the same text disclosed in the other Joshi patent,
19 the '376 patent, which was DTX 1000?

20 A. Yes.

21 Q. And you understand the specification of these two patents
22 to be substantially the same?

23 A. Yes.

24 Q. And what would a person of ordinary skill in the art
25 understand from this statement in the Joshi patents?

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1 A. So up until this time, looking at the literature of what's
2 been reported in psoriasis with BG-12, what's been reported in
3 studies of psoriasis in MS with different versions of dimethyl
4 fumarate, whether it be Fumaderm or DMF as a monotherapy or
5 specifically DMF as a microtablet, there's a very consistent
6 pattern of side effect profiles that are seen in all of these
7 different formulations of the drug.

8 Q. And, Dr. Greenberg, are you aware that there's a statement
9 in the '999 patent in DTX 1001 that Biogen asserts would teach
10 a skilled artisan that Joshi ties tolerability of the drug to
11 the high concentration in the GI mucosa, not due to the
12 frequency or the total daily dose?

13 A. Yes.

14 Q. And let's see if we can find that statement. I believe it
15 is Column 5.

16 And do you agree with that interpretation of the Joshi
17 patent?

18 A. No.

19 Q. And why not?

20 A. So what's being indicated here is "The ingredients in the
21 tablet are released in the intestine in a concentration which
22 is too high, causing local irritation of the intestinal mucus
23 membrane."

24 And so when they're talking about side effects, it's
25 relative to that mucous membrane; it's not relative to

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1 absorption or anything along those lines.

2 Q. Again, does the skilled artisan, are they aware of any
3 additional -- excuse me.

4 Understanding that criticism or that teaching, supposedly,
5 of the Joshi patent and your understanding of it, what does
6 that actually mean, the GI mucosa that is not absorbed?

7 A. That, as you're dosing, every time you expose the GI
8 mucosa to the agent, you're risking the side effects. So part
9 of what this teaches is moving towards the twice-daily dosing
10 versus three-time-a-day dosing, because at three times a day,
11 the experience of the patient will be repeated 50 percent more
12 with than just having that extra dose.

13 Q. And a little bit before the break we also were looking at
14 the ClinicalTrials.gov website, and that was DTX 1135 on
15 page 2, if we look at the bottom of that page.

16 And what does the ClinicalTrials website explain about the
17 side effects for DMF?

18 A. So the ClinicalTrials.gov website does two things. One,
19 it recognizes the types of side effects that patients were
20 being expected to have, similar to what's been seen and
21 described already, the flushing and the nausea and the GI
22 symptoms; and it goes on to say that "Dose reduction will be
23 allowed for subjects who are unable to tolerate the
24 investigational drug."

25 Q. Now, would you agree that maximizing efficacy is the top

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1 priority for MS therapy?

2 A. So it's a complicated question. So at a philosophical
3 level, it's a great statement that I have to agree with. It's
4 like my mother and apple pie. Yes, I want to maximize therapy
5 for multiple sclerosis.

6 But you have to put it into the context of are we talking
7 about at a population level or an individual patient level?
8 And then you also have to put it into context with what the
9 patient experiences relative to side effects.

10 And so could I maximize efficacy in MS by giving every
11 patient a bone marrow transplant? I could, but that wouldn't
12 seem reasonable in a population level.

13 So when we're talking about maximizing therapy, it's a
14 complicated concept that can't be just whittled down to one
15 statement. We have to balance effective doses that are
16 effective for the majority of, or at least, I should say, a
17 significant number of the population studied, a meaningful
18 number of the population studied. And then you have to balance
19 that efficacious dose with are they going to take the drug?
20 Are they going to be compliant? Are they going to experience
21 side effects? And put that all together to pick a dose that
22 would work at a global level, even if it doesn't work for every
23 possible person.

24 Q. And you mentioned compliance. So let's talk a little bit
25 more about compliance. What is compliance?

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1 A. So compliance is when we actually follow the prescription
2 as it's prescribed. So if we're supposed to take a medication
3 at certain times a day or in certain doses or certain
4 frequency, we follow those instructions.

5 Q. Can the frequency with which a drug has to be taken impact
6 patient compliance?

7 A. Yes.

8 Q. How?

9 A. So there's both literature to suggest, common sense, and
10 my experience, that, as the frequency of dosing increases of
11 any medication, especially in a given day, compliance can go
12 down.

13 Q. And did you rely on any articles to support this notion
14 that, with less frequent dosing, compliance increases?

15 A. Yes.

16 Q. Can we look at DTX 1073? Or Slide 45, rather.

17 And on Slide 45, I believe, is the cause of the Paes
18 reference. Are you familiar with that?

19 A. Yes.

20 Q. Is this one of the articles you relied upon for
21 compliance?

22 A. Yes.

23 Q. What is DTX 1073 as shown on -- in general and also as put
24 up on Slide 45?

25 A. So this is a peer-reviewed publication published in

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1 October of 1997 by Paes and colleague entitled "Impact of
2 Dosage Frequency on Patient Compliance."

3 Q. What did Paes study?

4 A. Paes looked at the impact of dosage frequency on
5 compliance of patients who were receiving medications from
6 pharmacies.

7 Q. How frequently were the patients receiving it?

8 A. Patients could be receiving medications -- could be being
9 prescribed -- excuse me -- medications to take once a day, two
10 times a day, three times a day in various forms.

11 Q. And what about the Paes 1997 study -- what were the
12 results of it?

13 A. So what they showed, as highlighted here on the slide,
14 DDX 1100, Slide 45, is in this study the data showed a clear
15 relationship between compliance and the number of daily doses.
16 And they end by saying "The compliance increases with a
17 reduction of the number of doses."

18 Q. Does that comport with your experience in treating
19 patients with MS?

20 A. It does.

21 Q. And you mentioned another article. If we could turn to
22 the next slide. It's highlighting an article by Eisen.

23 Did I pronounce that right?

24 A. I haven't met him personally. I think it's Eisen.

25 Q. Dr. Eisen from 1990.

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1 What is DTX 1039?

2 A. So this is a publication entitled "The Effect of
3 Prescribed Daily Dose Frequency on Patient Medication
4 Compliance."

5 Q. In which journal did it appear?

6 A. So this appeared in the Archives of Internal Medicine.

7 Q. And what did the results of Eisen 1990 show?

8 A. So in line with what was concluded in the Paes publication
9 we previously reviewed, Eisen and colleagues indicated that
10 "Compliance improves dramatically as prescribed dose frequency
11 decreases. Improved compliance" -- it goes on to say "What
12 health care providers can do to improve compliance is to select
13 medications that permit the lowest daily prescribed dose
14 frequency."

15 Q. And so, in your opinion, is the skilled artisan going to
16 be looking for or motivated to have a more compliant dosing
17 regimen when approving unknown therapies?

18 A. Absolutely, particularly in multiple sclerosis. As we've
19 talked about today and even hearing in the openings, this
20 notion of there can be an invisible component to the disease.
21 Anything we can do to improve compliance is a heavily
22 motivating factor when picking a dosing regimen.

23 Q. And also you had, on your motivation overview, you had
24 mentioned 120-milligram intervals of the drug that was
25 available. Turning to slide -- the next slide, why are you

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1 talking about 120-milligram-a-day intervals?

2 A. So in the literature, whether we're talking about
3 Fumaderm, studies that looked at DMF as a monotherapy, or
4 studies that specifically looked at BG-12, all prior to 2006,
5 all of the studies utilized increments of 120-milligram doses
6 of DMF.

7 The Fumaderm tablets that would be available to a skilled
8 artisan were available with DMF as 120-milligram dose. BG-12
9 used capsules in 120 milligram increments, 120, 360, and 720 in
10 the arms taking multiple pills throughout the day.

11 And then in Nieboer, the dosing of DMF was in increments
12 of 120 milligrams at a time.

13 Q. To your knowledge, has a dose higher than 720 milligram
14 ever been tested?

15 A. Not to my knowledge.

16 Q. And so, as of this time -- again, we're probably about
17 2006, earlier than 2006 -- how would a skilled artisan be
18 motivated by compliance and side effects in the 120 milligram
19 intervals?

20 A. So, as we enter January of 2006, there's a combination of
21 having a strong reasonable expectation of success in this dose
22 range. That caps off at 720. And with that cap being dictated
23 by the literature showing side effects in multiple trials
24 amongst multiple formulations of dimethyl fumarate, the
25 Fumaderm label calling out a hard stop indicating that you must

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1 not go beyond that high dose, and the authors describing side
2 effects constantly indicating that seeking the lowest
3 efficacious dose, trying to avoid side effects, would all be
4 motivating.

5 And when you take all of that in a background of a world
6 where I can prescribe in 120 milligram increments and knowing
7 that I want a twice-daily equal dose, the math, the efficacy,
8 and the side effects would all take me and motivate me to use
9 480 milligrams. And I would be very reassured by the
10 experience of Schimrigk and Nieboer and Kolbach that I was
11 square-on from an efficacy perspective relative to the immune
12 system.

13 Q. And if we could turn to reasonable expectation of success.
14 Did you create a slide showing your opinions as to whether the
15 skilled artisan would have a reasonable expectation of success?

16 A. Yes.

17 Q. And what is that summary?

18 A. So I think it's important to note that prior to 2006 the
19 art that was available, the literature that was available,
20 could be broken down into two different ways.

21 First, looking at the autoimmune disease psoriasis and
22 recognizing that the psoriasis literature talks about multiple
23 sclerosis and the multiple sclerosis literature talks about
24 psoriasis, that there was this commonality between the two
25 autoimmune diseases. There's literature specifically about

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1 480-milligrams a day showing a clinical effect to patients. So
2 I know I have this marker that that dose in a Th1-predominant
3 autoimmune disease led to a clinical benefit of patients.

4 But beyond that, in specific studies relative to multiple
5 sclerosis, I get ample evidence to suggest that that dose range
6 of 360 to 720 was efficacious. Between Schimrigk and the
7 prolonged exposure to 360 milligrams and then the press release
8 in light of the abstracts and the posters of Kappos, I would
9 know that up to 720 milligrams had been efficacious.

10 And, finally, when looking to that autoimmune disease
11 world of psoriasis, there had been twice-daily dosing, BID
12 dosing. So from an immune system point of view, in order to
13 shift that immune system from a Th1 to a Th2, giving
14 240 milligrams twice a day was able to achieve that goal in
15 actual patients.

16 So putting this all together, I think it's very fair to
17 say I'd have a reasonable expectation of success moving forward
18 with 480 milligrams of dimethyl fumarate in multiple sclerosis.

19 Q. Is that true even though you're really just trying to sort
20 of cherry-pick some psoriasis 480 milligrams and shove it into
21 the MS theater?

22 I mean, is that really going to provide a skilled artisan
23 with a reasonable expectation of success?

24 As you said, these are complex, very difficult diseases.
25 How can you do that?

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1 A. It's a good question. And I understand why, on its face,
2 it seems like I'm talking about apples and oranges, because, as
3 has been said, psoriasis is a skin disease; multiple sclerosis
4 is a brain disease. These don't -- you go to a dermatologist
5 for psoriasis; you go to a neurologist for multiple sclerosis.

6 But the common link between both of them, and what has
7 evolved since the 1980s and 1990s, is recognizing that you go
8 to those clinicians because of the end organ damage. I know
9 how to manage the symptoms of multiple sclerosis. I know how
10 to do MRIs. I don't do biopsies of skin. I don't do
11 psoriasis. Dermatologists do that.

12 But what we share in common, even though you wind up at
13 two different clinics, is the autoimmune profile which had been
14 theorized to be similar actually proved to be similar for a lot
15 of patients, not all. This is a complex disease. But in the
16 setting of multiple sclerosis, if I can have a reasonable
17 expectation of success that it will benefit an appropriate
18 proportion of a population, a meaningful proportion of a
19 population, then I would definitely take the expertise and the
20 experience from psoriasis and apply it to multiple sclerosis.

21 Q. And in all of your work in preparing your opinions and
22 everything that went into it, did you ever come across anything
23 that would teach you that 480 milligrams would not work?

24 A. I'm not aware of anything that would say that.

25 Q. Were there any prior articles or anything that said you

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1 got to go to 1500?

2 A. I'm not aware of any.

3 Q. Now, even if the psoriasis data is not relevant, even if
4 perhaps the Court disagrees with you and says maybe not
5 psoriasis, too big of a stretch, would you still believe that
6 there was a reasonable expectation of success that
7 480 milligrams would work?

8 A. I would.

9 Q. Why?

10 A. So as we move into specifically multiple sclerosis -- so
11 if I was sitting here today and the only studies that had ever
12 been done were psoriasis, I would still believe that I'd have a
13 reasonable expectation of success because I think the data
14 comparing the two is adequate and convincing.

15 But in the prior art prior to 2006, I have reports of two
16 different studies, one a well-done, over-a-year-and-a-half-long
17 study in a small number of patients and one study in a large
18 number of patients over a short period of time. So two kind of
19 versions of studies in multiple sclerosis showing efficacy of
20 dimethyl fumarate in this range of 360 to 720.

21 And so even if I knew I wanted to be in that range and
22 minimize side effects and do twice-a-day dosing, I would still
23 get to 480 milligrams.

24 Q. And so I think that if we can turn to the next slide,
25 Slide 49, just overall looking at your pathways to

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1 obviousness -- and briefly because we've gone over a lot of
2 things today -- why, in your opinion, would the combination of
3 the January 2006 press release and the Schimrigk 2004 abstract
4 render the claims of the '514 patent obvious?

5 A. So with just the January 2006 press release and the
6 Schimrigk 2004 abstract, I have on one hand a publicly
7 available piece of art indicating that dimethyl fumarate as a
8 monotherapy reached its end point of treating multiple
9 sclerosis at at least a 720-milligram dose.

10 And on the other hand, I have a well-done trial using
11 dimethyl fumarate dosed as Fumaderm, but in the abstract
12 referencing that Fumaderm relative to the amount of DMF the
13 patient is exposed to, showing a prolonged period of remission
14 of patients at a dose of 360 milligrams.

15 And so putting those two together, I would find a claim
16 that 480 milligrams would be effective to treat MS as an
17 obvious claim in light of these two pieces of work.

18 Q. Okay. So let's turn to the second ground.

19 MS. BLOODWORTH: And, Your Honor, just for education,
20 all of this art up till this point has been 102(b) art. It's
21 all published one year prior. So now we're going to move into
22 the Kappos presentation and the Kappos 2004 abstract, the
23 second ground.

24 BY MS. BLOODWORTH:

25 Q. So, Dr. Greenberg, what is the Kappos presentation?

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1 A. So the Kappos 2006 presentation is the presentation of the
2 data from the Phase 2 Biogen-sponsored study of BG-12 in
3 relapsing-remitting multiple sclerosis patients.

4 Q. And for the record, it is JTX 2153. And what is the
5 presentation titled?

6 A. So the title of the presentation is "Efficacy of a Novel
7 Oral Single-Agent Fumarate, BG-12, in Patients with
8 Relapsing-Remitting Multiple Sclerosis: Results of a Phase 2
9 Study."

10 Q. And how many authors are on the publication?

11 A. So there are 14 authors by my quick count.

12 Q. And are you aware that it was presented at the European
13 Neurological Society meeting?

14 A. I am.

15 Q. And approximately how many people attend those meetings?

16 A. To my understanding, there's, on average, a couple
17 thousand patients at that meeting -- excuse me -- a couple
18 thousand practitioners, not patients.

19 Q. And who is the first-named author of the presentation?

20 A. Dr. Kappos.

21 Q. And what, in your experience with clinical trial, is the
22 first author typically responsible for?

23 A. So the first author is usually involved in both the
24 design, acquisition, analysis, and critical review of the data
25 in preparing a presentation for a public meeting such as this.

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1 Q. And also in your experience, ethically, if you present a
2 paper or an author on the paper, are there certain obligations
3 on you?

4 A. We are required to certify that we had access to data,
5 that we are representing the work as us being involved in the
6 work in a meaningful way, meaning I'm not allowed to correct
7 grammar on a paper and be an author. The standard is that you
8 played a meaningful role in the design, conduct, or analysis of
9 the trial.

10 Q. And who gave the presentation?

11 A. To my understanding, it was Dr. Kappos.

12 Q. And do you have an understanding of Dr. Kappos's role for
13 the Kappos study?

14 A. My understanding is that he served as a steering committee
15 head for the study.

16 Q. And let's look at the background of the presentation. And
17 this is slide -- DDX 1100, Slide 52.

18 What did the Kappos presentation describe?

19 A. So through this presentation, I'll draw attention to a
20 variety of things that stand out to me.

21 On this slide in the background I think it's worth noting
22 that, when describing -- and I'll point on the screen over
23 there -- the background about fumaric acid esters, it refers to
24 a Th1 to Th2 cytokine profile shift. And it has a citation
25 cited Number 8, which is an article by Ockenfels.

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1 And specifically what this says to me is that the authors,
2 including Dr. Kappos, recognized the role of the Th1/Th2 immune
3 system paradigm in multiple sclerosis, and they were pulling
4 from the psoriasis literature of fumarates showing efficacy via
5 shifting a Th1/Th2 cytokine profile.

6 Q. The Ockenfels reference, Number 8 on Slide 52, that is the
7 Ockenfels 1998 reference that we talked about earlier in your
8 testimony?

9 A. Yes.

10 Q. So why do you think Biogen would mention psoriasis studies
11 in the background slide of the Phase 2 study?

12 A. I think, as you're giving background for any study, you
13 display all of the different things that got you to the point
14 for considering the study. And this is recognition of what
15 we're identifying in the prior art, that this was a
16 long-standing connection, a known connection between the
17 immunology of psoriasis and multiple sclerosis, and that you
18 could pull from the psoriasis experience into multiple
19 sclerosis. And that's being based on prior art; it's not being
20 based on data presented here.

21 Q. Is there a slide on the role of fumaric acid therapy?

22 A. There is.

23 Q. If we could turn to Slide 11 of JTX 2153.

24 What does it say about fumaric acid therapy?

25 A. So the title of the slide was "Fumaric acid therapy has

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1 shown efficacy in immune disorders." And after noting that
2 it's orally bioavailable, which is basically just saying we
3 don't need to give a shot, it goes on to note two things and
4 two things only.

5 First is that it has successfully been used for long-term
6 treatment of psoriasis. And it was successfully used in a
7 trial of relapsing-remitting multiple sclerosis leading to a
8 significantly reduced number of gadolinium-enhancing lesions in
9 ten patients.

10 And that's referencing the Schimrigk paper -- the
11 Schimrigk abstract and poster and body of work that we've
12 previously spoken about.

13 Q. And so that's reference -- Footnote 4 is the Schimrigk
14 study?

15 A. Yes.

16 Q. And it cites the Nieboer article, the Nieboer 1990
17 article, for example, for the point of it being successfully
18 used for long-term treatment of psoriasis?

19 A. Yes.

20 Q. And that's the same Nieboer 1990 article that we've
21 discussed a couple times in your testimony?

22 A. Yes.

23 Q. So what does the Kappos 2006 presentation say about
24 efficacy of BG-12 and psoriasis?

25 A. So it starts off, before getting to any of the data about

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1 what was experienced by patients in this Phase 2 trial, by
2 anchoring dimethyl fumarate as an effective therapy in both
3 psoriasis and multiple sclerosis prior art.

4 Q. And is it reference -- is reference to the Morwitz 2005
5 article that we've discussed in your testimony?

6 A. Yes.

7 Q. And what was the design of the study?

8 A. So as outlined on this slide, which is DDX 1100, Slide 55,
9 the design of the study was one that would determine the
10 efficacy of BG-12, dimethyl fumarate, on brain lesion activity
11 in relapsing-remitting multiple sclerosis patients.

12 After defining the inclusion criteria, which is standard
13 for these trials, it listed the end points and highlighted what
14 was the primary end point, specifically, the total number of
15 new gad-enhancing lesions on MRI scans performed at weeks 12,
16 16, 20, and 24.

17 Q. And does the Kappos 2006 presentation provide a schematic
18 of the study design?

19 A. It does.

20 Q. If we could turn to Slide 15 of JTX 2153.

21 And what is shown in Slide 15 of the Kappos presentation?

22 A. So what's shown in Slide 15 of the Kappos presentation and
23 Slide 56 of what we're talking about now is the schematic of
24 what was planned and what was executed for this Phase 2 trial
25 of BG-12 in multiple sclerosis.

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1 Q. And how many dose -- what were the doses that were
2 administered in this study?

3 A. So, as had been noted in the past, the study included four
4 arms: a placebo arm and then three different doses of BG-12,
5 120 milligrams a day, 360 a day, and 720 a day.

6 Q. And to state the obvious, there was no 480-milligram dose
7 in the study, correct?

8 A. There was no 480-milligram dose in the study.

9 Q. Okay. And what are the little brains on the bottom of the
10 schematic representing?

11 A. So those graphics represent the time points at which the
12 study would acquire MRI data from patients. And specifically
13 noting they would get an MRI at week 4, 8, 12, 16, 20, and 24.

14 Q. So a total of -- is it six scans?

15 A. Six scans. It was monthly scans over the six months.

16 Q. And what does it say about tolerability?

17 A. And so the bottom of the slide indicates that patients
18 received 120 milligrams TID, which is three times a day, during
19 the first week to determine tolerability.

20 Q. So was tolerability side effects still an issue with DMF
21 as of the Kappos -- the time of the Kappos presentation, in
22 your opinion?

23 A. Yes.

24 Q. Can you please walk us through how patients are typically
25 screened for participation in a study and then how they are

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1 assigned to different arms?

2 A. Yes.

3 So the screening phase, as outlined on the schematic,
4 refers to the period of time in a study where we do several
5 things with a patient.

6 First, we review the inclusion-exclusion criteria. Do
7 they have multiple sclerosis? Do they meet the criteria of how
8 many relapses they've had? And then we also look to make sure
9 there aren't any medical comorbidities or other reasons why
10 they wouldn't be able to participate in the trial.

11 Once somebody has, obviously, signed informed consent and
12 passed screening, then we move to the randomization stage of a
13 study, which is a critically important part setting up into
14 motion ultimately the data analysis at the end.

15 Q. Is this how patients get assigned to be on which arm of
16 the study?

17 A. It is. In a nonrandommized trial, if I had ten patients
18 come to me in a nonrandommized trial and there were multiple
19 arms, I could just assign which patient I wanted to go into
20 which arm. But that's been proven to be problematic from a
21 data interpretation perspective because of biases. I would
22 naturally pick the sickest patient to go to the highest dose if
23 I thought that was going to be best, for example.

24 And so randomization is there such that, as patients come
25 into a clinical trial center or a clinic, they can be assigned

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1 an arm in an unbiased fashion such that, when we get to the end
2 of the study and we're comparing the different arms, we're
3 comparing apples to apples, that we didn't just have one type
4 of patient in one arm or another, that it was an equal
5 distribution of patients across the four arms.

6 Q. And how many patients were a part of this study?

7 A. So as outlined on the next slide, which is DDX 1157, there
8 were 309 patients screened. 257 were randomized into one of
9 the four arms.

10 Q. And looking at Slide 17 of the Kappos presentation,
11 JTX 2153, after the randomization, what does the Kappos
12 presentation tell the skilled artisan about the baseline
13 patient characteristics of each arm?

14 A. So in a standard fashion for presentations for clinical
15 trials that are randomized, there is a slide like this showing
16 how the randomization occurred and were the patient groups
17 equal.

18 So across the top of the slide, you have the four
19 treatment groups. And it lists the placebo arm and the three
20 doses and how many patients were in each. And you see it's
21 about an equal number. It's 65, 64, 64, and 63.

22 And then the slide goes on to summarize a few
23 characteristics of the patients so that you can compare, just
24 visually sitting there, did the randomization work? Do you
25 have the same types of patients?

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1 You want to make sure, for example, in age, that we didn't
2 enroll a lot of 18-year-olds in the 720-milligram group and a
3 bunch of 35-year-olds in the placebo group because maybe age
4 would skew the data.

5 And as we see here, age was very similar across the four
6 groups. And just by eye, it's obvious that there weren't
7 distinct differences between them.

8 It goes on to compare the patients based on clinical
9 characteristics. And they picked two, the most common two,
10 which are the relapse history, meaning in the last year or, in
11 this case, last three years, how many relapses had patients
12 had? Were we enrolling patients who had had ten relapses this
13 past year in one arm versus none in another arm?

14 And what you see are numbers that are very consistent
15 across the four arms. One relapse in the last year and two or
16 three relapses over the last three years over the arms. And
17 just by eye, you'd see that these are very balanced four arms
18 for a clinical study.

19 The third criteria that gets used is referred to as the
20 EDSS. That's an acronym that's defined below, the expanded
21 disability status scale. And that's a disability score that we
22 use in multiple sclerosis. It's just a score that's zero to
23 ten. And the higher your number, the more disabled you are.

24 And so they report the average score so that you could
25 look at the data and say the patients from a disability

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1 perspective, when they started the study, were or were not
2 similar. And as you move across the four arms, you see a
3 disability status score average that's very similar, all
4 hovering around 2.5 range, which is very even across the four
5 arms.

6 And then the last criteria that they use is the number of
7 gadolinium-enhancing lesions, the average. In this one, there
8 is a difference between the arms.

9 Q. So to recap, the age, relapse history, and EDSS scores --
10 EDSS baseline characteristics are all fairly consistent?

11 A. Yes. They look to be very consistent. And nothing would
12 stand out to me in terms of differences.

13 Q. And are the groups similar relative to their mean baseline
14 GD-enhancing lesions, in your opinion?

15 A. They are not.

16 Q. And why would having a difference in the baseline of the
17 GD-enhancing lesions matter?

18 A. It matters for several reasons.

19 So the first is -- and the foremost is -- this was the
20 primary end point of the trial. The data in the a priori
21 decision on data analysis was going to be how many
22 gadolinium-enhancing lesions do people have at the end of the
23 trial.

24 And so if you have a group that is starting off with far
25 fewer or far higher, then you are handicapping them relative to

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1 the outcome of the trial. It would be like enrolling patients
2 in a trial for hypertension.

3 And if in one arm the average blood pressure was 200/100
4 and in the other arm the average blood pressure was 140/90,
5 even if the drug worked in both arms, at the end of the study,
6 the people who started at 140/90 are going to look better. It
7 sets you up for having a discrepancy at the end.

8 Q. And did you create a demonstrative graphing this
9 discrepancy?

10 A. Yes, I did.

11 Q. And if we can look at slide -- DDX 1000, Slide 59, what is
12 depicted here?

13 A. So what's at the bottom of the slide is just a blowing up
14 of the data from the Kappos trial, just showing the mean number
15 of gadolinium-enhancing lesions in the four patient
16 populations.

17 So the average number of gadolinium-enhancing lesions in
18 the placebo arm was 0.8. In the arm that was randomized to
19 receive 120 milligrams a day, it was 1.2. In the group that
20 was randomized to receive 360 milligrams a day, it was 2.5.
21 And then in the 720-milligrams-per-day dosing arm, it was back
22 down to 1.2.

23 So when you just graph this to visually see are these
24 groups similar, are we comparing apples to apples, is everybody
25 starting off from equal footing, visually, you can see that the

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1 360-milligram arm stands out.

2 And it's important to note, just from the purposes of a
3 skilled artisan, the graph isn't necessary. I add this just to
4 demonstrate what goes through my mind when I see numbers like
5 that.

6 Because when I look at the placebo arm compared to the
7 360-milligram-a-day arm, the 360-milligram-a-day arm was three
8 times higher than the placebo, but the 720 and 120 were pretty
9 close. And so if we're going to measure gadolinium-enhancing
10 lesions over the course of the trial, that 360-milligram-a-day
11 arm is being handicapped from the get-go. The randomization,
12 unfortunately, had what we refer to as a chance bias.

13 Q. So is -- and I guess maybe I cut you off.

14 But so the imbalance in these baseline lesions, this three
15 times difference over placebo, how does that occur? I mean,
16 how do you let that occur in a clinical trial?

17 A. So it's important to note that I actually don't fault the
18 design of the clinical trial. I don't fault the study
19 personnel. This is something that can happen in trials.

20 So there's two types of biases that we can have in trials.
21 One is that systematic bias I referred to, which is why we
22 randomized. Systematic bias is if I take all of the patients
23 with a severe version of disease and I put them into the
24 highest-dose category. That's a systematic bias.

25 Chance bias is by no fault of the investigator. As we

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1 were randomizing in this trial, the investigators didn't use a
2 baseline MRI as one of the characteristics to randomize. It's
3 not required. I don't fault them for not doing it. I think
4 they did a wonderful job in terms of design and execution of
5 the study.

6 But when it comes to chance bias, what the tenets of
7 clinical trial data interpretation indicate is you have to deal
8 with it at data analysis. You have to correct for the impact
9 of a chance bias in how you interpret the results.

10 Q. So you're saying this baseline characteristic imbalance,
11 it was caused by bad luck?

12 A. Literally bad luck.

13 Q. And is this something that is -- again, can happen in
14 clinical trials? Is it a known phenomenon?

15 A. Absolutely. When we take part in courses training
16 trainees who are learning to be clinical trialists, this is a
17 discussion that gets had and is described throughout the
18 literature of chance bias affecting an unequal randomization.

19 Q. And what is the significance of unequal randomization on
20 the interpretation of trial data?

21 A. So it depends on what was unequally randomized.

22 So, for example, if I was doing a trial on multiple
23 sclerosis and I found out in the randomization I had an
24 overrepresentation of left-handed individuals in one treatment
25 arm, I might not care. That might not be a significant unequal

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1 randomization to pay attention to.

2 But when the unequal randomization is relative to the
3 primary end point of the trial, it has to be recognized and
4 dealt with in data interpretation.

5 Q. And so the number of mean gadolinium-enhancing lesions is
6 the primary end point of this trial?

7 A. The primary end point is the new -- the mean of new
8 gadolinium-enhancing lesions over weeks 12 to 24. So it is the
9 primary outcome.

10 Q. And what does the Kappos 2006 presentation report about
11 the results of the primary end point?

12 A. So on the slide shown here, which is DDX 1100 Slide 60, it
13 shows, as we've seen earlier today, the outcomes as presented
14 by Dr. Kappos at this meeting showing the mean number of new
15 gadolinium-enhancing lesions from weeks 12 to 24, what was
16 called the prespecified primary end point.

17 And so they're basically saying, in the trial design, we
18 said we were going to do X analysis, and here it is, just the
19 data as it was acquired. And it shows that the placebo arm had
20 the highest number of mean number of new gadolinium-enhancing
21 lesions. The next arm, 120-day, had lower. The 360-a-day
22 looked slightly lower. And then the 720-milligrams-a-day was
23 the lowest. And they point out that that was a statistically
24 significant reduction of gadolinium-enhancing lesions compared
25 to the placebo arm.

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1 Q. Does the data show a trend for the 360-milligram dose, in
2 your opinion?

3 A. So just visually as you go from left to right, the bars
4 get lower. They don't talk about statistical analysis or
5 statistical trends. And so, just visually, you see it getting
6 lower. But that's all you can say.

7 Q. And do skilled artisans require statistical perfection
8 before they'll rely on data in a clinical trial?

9 A. They don't require statistical perfection. You want
10 people to interpret their data within the bounds of the trial
11 they're doing. And so you can look to see if you feel as
12 though the analysis was complete or incomplete. And you can
13 look to see, in the context of the trial, what was the trial
14 powered to look at and how were the conclusions analyzed in the
15 conversation?

16 Q. And did the Kappos results take into account the baseline
17 imbalance?

18 A. So as presented here, they did not.

19 Q. And if we can turn to DDX 1161.

20 What is this comparison? It looks like it's -- on the
21 bottom box is the baseline characteristics, and the top box is
22 the results. What is the purpose of this line?

23 A. So the purpose of this is just to take the data that was
24 presented at baseline characteristics and put it in respect to
25 what's being presented as the prespecified primary end point.

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1 And to show that that third arm that was getting shorter, was
2 getting smaller as you move from left to right, as that
3 360-milligram was somewhere in between 120 and 720 a day in an
4 unadjusted fashion, that it's that arm that suffered from being
5 unequally randomized.

6 They started off twice as active in terms of their MRI as
7 the 120-a-day or 720-a-day. They started off three times as
8 active compared to placebo. And yet despite that handicap at
9 the baseline, they were still in between the 120- and
10 720-a-day.

11 Q. And does the Kappos presentation report anything about
12 relapse rates?

13 A. It does. As had been described in the trial description
14 previously, they were going to report on what are called
15 secondary outcomes. So the study will routinely look at what's
16 called an annualized relapse rate in an MS population and
17 report the data.

18 Q. And what is an annualized relapse rate?

19 A. So an annualized relapse rate is basically counting how
20 many relapses are happening per year in a population of
21 patients.

22 So you take a group of patients, you follow them for a
23 year. Let's say it was ten patients. If, amongst them, there
24 were ten relapses over the year, the annualized relapse rate
25 would be one. On average, there was one relapse per year in

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1 this population.

2 And it's a data point that gets used by regulatory
3 agencies when considering FDA approval for disease-modifying
4 therapies.

5 Q. And how long was the Kappos Phase 2 study?

6 A. So this was a Phase 2 study which was designed to be
7 short. It was only six months, and hence used MRI as a primary
8 outcome, not annualized relapse rate.

9 Q. And what was reported about the annualized relapse rates
10 in the Kappos presentation?

11 A. So in this slide -- which again is DDX 1100, Slide 62,
12 which is just a recreation. We didn't add circles or boxes or
13 anything. This is the original presentation -- they report out
14 the numbers in terms of the annualized relapse rates between
15 the four arms. And they circle the 720-milligram-a-day arm and
16 the annual -- the placebo arm, noting that the 720-milligram
17 arm had an annualized relapse rate of .44 and the placebo arm
18 had one of .66.

19 And at the bottom of the slide in the bottom left in very
20 small print, they do the math to say that this is a 32 percent
21 reduction versus placebo.

22 Q. And what about -- so let's back up.

23 How did each arm do in the annualized relapse rate?

24 A. So these are, in terms of annualized relapse rate,
25 relatively similar. There's not a degree of magnitude,

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1 dramatic magnitude difference in the arms. What's notable, as
2 you move from left to right, the placebo had an annualized
3 relapse rate of .66.

4 The 120-milligram-a-day arm actually had the lowest
5 annualized relapse rate of all the doses. It was 0.42 and
6 would actually have the highest percent reduction compared to
7 placebo even greater than what was seen in 720 milligrams a
8 day.

9 In the 360-milligram-a-day arm, it's in the same range.
10 It is the highest at 0.78 but still within the range of all the
11 other arms.

12 In the 720-a-day was 0.44. But I have to caution, as the
13 authors do and as the trial outline does, this study is not
14 powered to make statistical conclusions relative to annualized
15 relapse rate.

16 So this is a teaser, if you will, to skilled artisans.
17 It's to give a sense of about what the annualized relapse rate
18 is while on drug, and it can help with thinking about trials or
19 studies in the future, but it's not a conclusive study relative
20 to relapse rate.

21 Q. So reading the Kappos presentation and the 32 percent
22 reduction in relapse rates, would you find that underwhelming?

23 A. No.

24 Q. Why not?

25 A. So 32 percent reduction versus placebo, when you take what

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1 you're seeing in entirety, the primary end point and the
2 secondary end point, tells us that we're in the right range for
3 treating patients.

4 In a Phase 2 trial, which is short, it is very difficult
5 to look at annualized relapse rate and get excited or depressed
6 or up or down. The point of the Phase 2 trial is to help with
7 dosing, dose selections, it's going to look for safety signals,
8 and to get the hint of efficacy from the MRI data which was
9 their primary end point.

10 Q. So the 32 percent reduction rate wouldn't prompt you, as a
11 skilled artisan, to dose higher than 720 milligrams?

12 A. No. So in this study, which was a dose-ranging study that
13 went from 120 to 720, I'm seeing a efficacy signal -- if that
14 is a sign, if you will, if I'm supposed to look at annualized
15 relapse rate as a way, in a Phase 2 study, to point the way,
16 then I have to ask why didn't we circle the 120-milligram arm?
17 It has the lowest annualized relapse rate.

18 The point of this slide is to demonstrate that we're
19 seeing this change, but it's to remind us that we're not
20 powered to do this. But we are seeing efficacy on the primary
21 end point in the 360 and the 720 arm. So if I know I'm getting
22 efficacy in the 360-milligram arm, there's nothing to teach me
23 to go higher than 720.

24 Q. And so just as the 32 percent doesn't encourage you to go
25 higher, conversely, the results of the 120-milligram arm you're

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1 not relying upon for why you should dose lower?

2 A. No, again, because I stick by that mantra. It's designed
3 around the gadolinium-enhancing lesions. So I have to start
4 there, form a conclusion, and then consider the other data.

5 And when you correct for that imbalance that was there, it
6 becomes pretty obvious that, in that dose range of 360 to 720,
7 that's where we're seeing efficacy.

8 Q. And does this imbalance in the baseline permeate the other
9 end points in the study?

10 A. No. So, when we're talking about the imbalance, it was
11 very specific to the primary outcomes. So the primary outcomes
12 was gad-enhancing lesions, and that's where the imbalance was.

13 Q. If we can turn to the summary of the study. I'm a little
14 out of order. I skipped to Slide 65, real fast. You had
15 mentioned that the annualized relapse rate in the study was
16 disclosed as not being powered.

17 And so in the summary slide, does it address that? Does
18 it inform you of that information?

19 A. It does. The very last sentence that the authors leave
20 the audience with of the entire study is "The study was not
21 powered for this end point," and it's referring to annualized
22 relapse rate.

23 The other just noteworthy point relative to the summary
24 slide is the first sentence, which references that BG-12 was
25 effective reducing brain lesion activity as measured by MRI in

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1 a dose-dependent manner.

2 Q. What does that mean, in a dose-dependent manner?

3 A. This is telling a person skilled in the arts what we
4 observed, that, as you increase the dose, the efficacy
5 improved, that there was a dose relationship. And as you --
6 what's not on this slide but would be obvious to a person
7 skilled in the arts is that that 360-milligram arm behaved very
8 similarly to the 720. And so there wouldn't be anything
9 pushing me to go past the 720. I'd be looking within these
10 ranges to optimize and pick a final dose.

11 Q. Do you agree with Biogen's expert's interpretation of
12 dose-dependent manner, that that just means the 720 works?

13 A. That's not the usual and customary use of the term
14 "dose-dependent manner." We're usually talking about a
15 relationship, as you move from doses, a change in efficacy.

16 Q. Would a skilled artisan think that in particular in a
17 trial that has multiple active arms?

18 A. They would think because, otherwise, you'd say the drug
19 worked at and name the dose that it worked. Using the term
20 "dose-dependent manner" has a different connotation than just
21 saying which dose worked.

22 Q. Okay. I'm going to turn back now to Slide 63. Slight
23 deviation.

24 What did the presentation report about side effects?

25 A. So the presentation had two slides talking about side

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1 effects, one entitled "Serious Adverse Events," which is what
2 we're looking at now in Slide 63, where it records how many
3 patients experienced an adverse event that led to the need for
4 additional medical therapy or hospitalization. So these are
5 considered the most serious of complications that can occur
6 during the course of a trial.

7 Q. And were nonserious adverse events also reported?

8 A. Yes. And that's in the next slide, which is DDX 1100,
9 Slide 64. The adverse events reported out by treatment group
10 is basically a tally of how many patients at any point during
11 the trial came in and reported to a study investigator some
12 adverse event.

13 Q. After reviewing the adverse events and the serious adverse
14 events data, do you still believe that side effects are an
15 issue for the skilled artisan?

16 A. I do. These numbers are very much in line with all of the
17 teaching we've gotten from psoriasis trials, previous MS
18 trials, the labels and patents, and all of the art leading up
19 to this. And this would be in line with side effects that we
20 see from dimethyl fumarate.

21 Q. And now we've discussed the failure of randomization. So
22 let's go back and look a little bit more about that in your
23 opinions on the impact of the Gd-enhancing lesion baseline.

24 Sitting in the audience of the Kappos 2006 presentation,
25 what would the skilled artisan's reaction be to the baseline

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1 characteristics?

2 A. So while the slide looks complicated, it's actually, in my
3 mind, a pretty simple two-step reaction, sitting in the
4 audience.

5 So step number one is seeing the imbalance between the
6 arms, seeing that the 360-milligram arm at baseline had a
7 distinctly different number of gadolinium-enhancing lesions.
8 And then, flipping to the need to say, given that it's a
9 primary outcome, I need to correct for that. And then taking
10 steps to correct for that.

11 Q. If you didn't, as a skilled artisan, actually do the math
12 to do the correction for it, would you still have a general
13 takeaway from the Kappos 2006 presentation?

14 A. Absolutely. And the point of the slide earlier, where you
15 take the baseline and show it relative to the prespecified
16 outcomes, it just gives you that intellectual reassurance that,
17 if you just want to eyeball it, if you will, that the 360 was
18 going to be significantly better than the placebo and the 120.

19 But you could go further with -- and this slide has
20 demonstrated here -- that, despite there being more than twice
21 as many baseline gad lesions for the 360 arm compared to 120,
22 it was doing better than 120; and despite having three times as
23 many as the placebo arm, it was doing better than placebo.

24 And so you really walk away with a very firm sense that
25 360 a day of dimethyl fumarate is effective for treating MS

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1 patients based on this outcome.

2 You could go further and do some math to try and sort out
3 if your hunch and if your eyeballing is, indeed, accurate. And
4 that's what's shown here.

5 Q. And so can you just -- let's walk through this slide. And
6 this is DDX 1066. And if we look up at the top box, can you
7 explain what is in the top box.

8 A. So this top table has four columns to it, the treatment
9 group, and then Column Number 2 is entitled the "Mean Number of
10 New Gadolinium-Enhancing Lesions, Week 12 to 24."

11 This is basically the primary -- the prespecified primary
12 outcome of the study. And it's the data to just say at the end
13 of the study of these four arms, when they counted up the
14 number of lesions and did the average over the population,
15 these were, as reported by the authors, the mean number of new
16 gadolinium-enhancing lesions.

17 The line next to that, which comes, again, straight from
18 the abstract, is what we saw at the baseline. And it's there
19 to show that, as you move from placebo to 120, you go from 0.8
20 to 1.2; very similar. But then, as you get to 360, it more
21 than doubles before going back down for the 720-milligram-a-day
22 arm at 1.2.

23 So those two arms are basically just taking the data from
24 Kappos and putting it in a tabular format. What we're seeing
25 is the imbalance expressed in the randomization on that third

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1 column.

2 And then you get to the math part, which is the fourth.
3 And it's basically saying let's correct for the imbalance. So
4 let's just subtract -- if you started with 0.8 lesions and you
5 ended with 4.5, let's just get rid of the 0.8 and see really,
6 during the course of the trial, what were the lesions that
7 formed while you were on the arm you were randomized to; let's
8 not carry whatever baggage you had at baseline forward in the
9 study.

10 So when you subtract 0.8 from 4.5, you get 3.7. So as you
11 move through that math, the corrected, the adjusted number of
12 mean gadolinium-enhancing lesions between weeks 12 and 24 that
13 occurred independent of the baseline is 3.7 in the placebo arm,
14 2.1 in the 120-milligram-a-day arm, 0.6 in the
15 360-milligram-a-day arm, and 0.2 in the 720-milligram-a-day
16 arm.

17 What's represented below it is a graph just showing those
18 numbers to, again, visualize that 360 and 720 were behaving
19 very similarly and really reinforce this notion of a
20 dose-dependent efficacy relative to dimethyl fumarate and
21 multiple sclerosis.

22 Q. If I understand this correctly, you subtracted the
23 baseline lesions out of each of the arms, so not just the
24 360-milligram?

25 A. No. I corrected each within their own group, you're

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1 correct. It was the placebo got corrected, the 120 got
2 corrected, the 360 got corrected, the 720 got corrected in a
3 unbiased, non-cherry-picking fashion. So it's just saying, if
4 I'm going to correct the 360, I have to do it for placebo, I
5 have to do it for 120, I have to do it for 720, and then
6 compare.

7 If those corrections led to the bars on the graph looking
8 very similar to the original presentation, which was the
9 prespecified end point, an uncorrected, unadjusted data set,
10 then you'd say, well, maybe correcting for the baseline
11 wouldn't change my conclusions.

12 But that's not what happens here. You can really
13 visualize the impact of that unequal randomization and show
14 that 360 and 720 are, in this study, clearly outperforming
15 placebo or the 120 milligram-a-day arm.

16 Q. And so what is the resulting takeaway of the trend in the
17 efficacy of the various arms from the Kappos 2006 presentation?

18 A. So when looking at this and correcting, it's reaffirming
19 of a lot of prior art, even before we get to here, which is,
20 when treating an autoimmune disease like multiple sclerosis, a
21 dose range of 360 to 720 milligrams works. It is going to be
22 effective.

23 And so, when we walk away and analyze the data
24 appropriately in the context of clinical trial data analysis
25 guidance, we find that the conclusion of the study was -- the

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1 conclusions reached were incomplete. That, even though
2 720 milligrams worked -- and I don't dispute that conclusion at
3 all -- we see that there was a lower dose that was working as
4 well.

5 Q. And would the skilled artisan need a statistical result of
6 the 360-milligram arm before they'd have a reasonable
7 expectation of success that it was being effective to treat MS?

8 A. No.

9 Q. And, obviously, Biogen's experts have some criticisms of
10 this, and one of which is that you just sort of, you know, did
11 some hocus-pocus hindsight and subtracted patients and you have
12 no idea what patients you were subtracting and how on earth
13 could you do this in any type of neutral or effective fashion.

14 Do you have any thoughts of that?

15 A. I'm aware and respectfully disagree.

16 Q. Why do you disagree?

17 A. So in the context of a population study, when we're
18 correcting for averages in the population, you don't have to
19 correct each individual patient to themselves. You take the
20 average and can do the correction just on the means. So not
21 having access to the individual patient data is not required.

22 Secondly, to suggest that a correction isn't required
23 breaks one of the fundamental tenets of clinical trial data
24 analysis on how to handle unequal randomization when a primary
25 end point is in play, particularly when a primary end point is

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1 in play.

2 And then, finally, while I am not a Ph.D. statistician,
3 the correction based on subtracting the baseline regions in an
4 unbiased fashion, correcting all four arms, not just correcting
5 the 360 and saying, look, it was the best, but correcting each
6 one independently to their baseline is honoring the fidelity of
7 keeping each group to themselves.

8 I'm not creating a new coefficient or a new model. I'm
9 doing relatively simple math. They may say it's too simple,
10 but it's an accurate and acceptable and unbiased approach to
11 correcting for this unequal randomization.

12 Q. Now, you were here for the opening arguments, I believe?

13 A. Yes.

14 Q. And you heard in the opening arguments that you didn't do
15 this until you were hired for this litigation. You published a
16 paper, in fact, that didn't have this baseline correction to
17 it.

18 If this was so obvious, why didn't you put this in your
19 paper?

20 A. Yeah. It's -- on its face, it's a good question, and I
21 can understand why it would beg credibility of why are we doing
22 it now?

23 If you look at the entirety of that paper, the point of
24 the paper was not analysis of clinical trial outcomes. If you
25 take the scope of the whole paper, it's kind of a review to

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1 clinicians of "Here are the different drugs that are in
2 different stages of development." It's a CliffsNotes version
3 of different molecules that clinicians should be aware of, and
4 it talks to the future and what we want to develop.

5 And so the point of the publication was not to reanalyze
6 data or suggest that it was a broad paragraph to say "This is a
7 drug; it looks like it's going to be effective; be aware;
8 coming soon to a theater near you" kind of thing.

9 And so if I had been asked at the time to write a paper on
10 data analysis of the clinical trials, this would have been one
11 of the first things we would have identified when analyzing
12 this trial.

13 Q. And is there another standard way of correcting for the
14 baseline imbalance that you also calculated?

15 A. There is another way.

16 Q. And let's go to DDX 1000, Slide 67.

17 Is this the other method you used to correct for the
18 imbalance?

19 A. Yes. So this is another method that was used, and it's a
20 little different, and division is always harder than
21 subtraction. So it takes a little more time to explain, but I
22 can walk through it.

23 Q. Let's focus on the top box and just show what it was --
24 what was the actual data input -- at data inputs and the
25 calculations you did.

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1 A. So the -- what is the second column of the table, the one
2 that has -- the first one with numbers in it, with data in it,
3 you see that we took the mean number of new
4 gadolinium-enhancing lesions -- again, this is the primary end
5 point of the trial. And one of the things to recall is this
6 was averaged over four scans.

7 So what the investigators did was at weeks 12, 16, 20, and
8 24, they did an MRI, they counted up all of the lesions over
9 four scans, and they said here was the average over those four
10 scans.

11 So what's done in the first column is to say let's look at
12 the average number of new lesions per scan. So if you had 4.5
13 lesions over the course of four scans in the placebo arm, when
14 you divide by 4, the average was 1.13 new lesions per scan.
15 And so it, basically, is saying let's look at the activity of
16 these patients on a per-scan basis instead of amortizing over
17 several months of the trial.

18 And then in the last column you still -- you're looking
19 for a method to correct for the unequal randomization. And so
20 in this situation, since the baseline scan was a single scan --
21 it wasn't an average over multiple; it was just one -- you can
22 create the ratio. And you can basically say how much more or
23 less active were patients on subsequent scans compared to their
24 baseline?

25 So, for example, in the placebo arm, it was -- the

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1 patients were 1.4 lesions more active per scan over the study
2 compared to the baseline. And, as you move down, you see that
3 those numbers drop. They go to .69 for the 120-milligram
4 dosing arm, .31 for the 360-milligram arm, and .3 for the
5 720-milligram arm.

6 And so what it says is that the 360 milligrams a day and
7 720 milligrams a day were noticeably less active over the
8 course of the trial compared to their baseline study.

9 Q. So did both of these calculations on Slides 66 and 67 just
10 affirm your sitting-in-the-audience view,
11 watching-the-Kappos-presentation sort of takeaway of the data?

12 A. Yeah. And so it's worth it, if I may, to look at this
13 again. This is DDX 1000, Slide 68.

14 So this is taking the primary end point data -- so how
15 many new gadolinium-enhancing lesions were seen over the weeks
16 of the study -- and putting below it what the baseline number
17 of scans were, what I have referred to as that handicap for the
18 360-milligram arm.

19 And so just looking at this, doing no math, no
20 subtraction, no division, no calculation, there is an obvious
21 need and potential impact of the unequal randomization that
22 occurred relative to the primary end point of the trial.

23 If the baseline of the gadolinium-enhancing lesions was
24 double that of the 720, it's going to have an impact. Doing
25 the math, taking the extra step, confirms what you see just by

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1 gestalt, if you will, sitting in and looking at the
2 presentation.

3 Q. Do you understand that Biogen's experts argue that this
4 baseline patient characteristics of number of Gd-enhancing
5 lesions is just fine? There's no problem? That you're the one
6 who's picking out a problem and trying to gerrymander some good
7 arguments?

8 A. I'm aware of that.

9 Q. And what do you think about that argument? Do you agree
10 with it?

11 A. I vehemently disagree with it. It's, as I've said, a
12 fundamental concept in clinical trials that an unequal
13 randomization should be recognized and accounted for in your
14 data analysis. It happens -- again, I don't fault the
15 investigators in any way, shape, or form relative to the
16 conduct of the trial. I just note that it is something that
17 should be noted in the data analysis and corrected for.

18 Q. Now, does it matter to you, though, that there were
19 dropouts during this study? Because, again, the baseline
20 lesion scan is a little bit of a different data set than the
21 end-of-the-day folks who were getting scanned.

22 Does that impact your opinions?

23 A. So at a broad level, we always consider the dropout rate
24 when we're trying to make conclusions relative to a trial. And
25 so you would look to the number of patients who dropped out and

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1 see if there were dramatic differences between the arms, which
2 in this study there were not.

3 And so given the fact that it was a relatively equal
4 completion rate amongst the four arms, it doesn't sway my
5 conclusion relative to needing to correct for the impact of
6 that correction on the baseline characteristics.

7 Q. Now, let's look -- we're still looking at Slide DDX 1000,
8 Slide 68. Looking at the reports on the 360-milligram arm, it
9 says "2.5 (4.22)."

10 And do you understand that the 4.22 is the standard
11 deviation for the mean number?

12 A. Yes.

13 Q. Does that have any impact on your opinions?

14 A. So in this setting it's definitely taken into account in
15 my opinion. You have to recognize the standard deviation
16 across these groups. When you look at the standard deviation
17 of that 360-milligram arm and the 720-milligram arm, which is
18 one of the important parts of anchoring, they're relatively
19 similar. The 720-milligram arm had a standard deviation of
20 3.52, which is in a very close proximity to the standard
21 deviation of the 360.

22 So I note it but recognize that it's not an anomaly that
23 would change my conclusions.

24 Q. But couldn't the standard deviation value represent a
25 bunch of outliers in the study?

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1 A. Yes, it could.

2 Q. What is an outlier?

3 A. An outlier is, if I enroll 60 patients into a study and
4 one of them behaves extremely difficult -- not difficult;
5 excuse me -- extremely differently, it can be difficult to
6 understand how do they relate to the larger group.

7 Q. And so you're not aware, though, that there are no
8 outliers, right?

9 A. There is always going to be a spread. And so, if you take
10 your 60 patients and take any characteristic -- their height,
11 their weight, their gad-enhancing lesions -- there's always
12 going to be somebody at the end of that range and at the bottom
13 of that range. And the question is is the degree of
14 outliers -- and we get a sense of that with the standard
15 deviation -- enough to dissuade us from making a conclusion?

16 And given the fact that those two arms had standard
17 deviations that approximate each other, it doesn't change my
18 conclusion.

19 Q. Now, the Gd-enhancing lesions are at baseline. And then,
20 again -- and then the scans are taken at four-week intervals
21 following the baseline scan, 12, 16, 20, and 24, I believe?

22 A. Yes.

23 Q. Now, what is the impact of the fact that Gd-enhancing
24 lesions, if any -- what is the impact, if any, if Gd-enhancing
25 lesions may disappear over time?

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1 A. I'm aware that that argument is being made, and it is
2 factually accurate that, when a patient has an enhancing
3 lesion, most of the time, if not always over time, it
4 disappears. It, as a single lesion, disappears.

5 But what that argument ignores is the significance of
6 gad-enhancing lesions on an MRI in MS as a prognostic factor
7 over the course of a study in terms of predicting future
8 gad-enhancing lesions.

9 So even though that one lesion may disappear, if you have
10 a population that has an obviously higher number of
11 gad-enhancing lesions, the data and the studies would suggest
12 that they would go on to have more lesions.

13 And that's what pushing a skilled artisan to correct for
14 the imbalance, because it's not an ignorable data point. It's
15 going to have an impact on the data interpretation.

16 Q. And so is it -- colloquially, would it be called the
17 patients on the 360-milligram arm are just more sick? They're
18 worse off when they're starting the study?

19 A. Especially in this primary end point, they were worse at
20 the beginning. And, when you look at the data in multiple
21 sclerosis, you would predict that they would be worse at the
22 end.

23 And so the fact that they weren't getting worse, the fact
24 that 360 kept them better than 120 and better than placebo
25 tells a skilled artisan that that dose is working.

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1 Q. And you mentioned a paper. Do you have a paper that
2 discusses this -- if you're sicker at the start, it's
3 prognostic of more disease state?

4 A. Yes.

5 Q. And let's look at JTX 2167. And I am not going to put the
6 name of the first-named author on the record because I don't
7 know how to pronounce it.

8 Why don't you do that, Dr. Greenberg.

9 A. The last name of the first author is Koudriavtseva, and
10 that's my best approximation. It is a paper that is published
11 in the Journal of Neurology, Neurosurgery, and Psychiatry in
12 1997, and the title is "Gadolinium-Enhanced MRI Predicts
13 Clinical and MRI Disease Activity in Relapsing-Relmitting
14 Multiple Sclerosis."

15 Q. And what does the -- what does JTX 2167 teach a skilled
16 artisan, in your opinion?

17 A. So, as shown on the slide here, Slide 69, the authors
18 found that "The number of enhancing lesions on the baseline
19 scan predicts the mean number of total and new enhancing
20 lesions during the follow-up period. The study suggests that
21 the number and volume of gad-enhancing lesions at a single
22 examination are strong, short-term predictors of subsequent
23 clinical and MRI activity."

24 Q. And so how is this relevant to your analysis of the
25 baseline imbalance in the Kappos presentation?

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1 A. So, if you take the first sentence of the conclusion, that
2 they find in the study that at baseline the number of lesions
3 you have will predict how many more lesions you're going to
4 have, and I enroll in a study two groups, one of whom has twice
5 as many baseline lesions at the beginning, assuming no impact
6 of drug or anything else, they're going to have more lesions at
7 the end.

8 And so from a clinical trials perspective, given that that
9 end number is your primary end point, you couldn't avoid
10 correcting for it. A skilled artisan would have to take that
11 into account when interpreting the conclusions of this
12 presentation.

13 Q. So did the 360-milligram arm in the Kappos presentation
14 just have an uphill battle?

15 A. They did. They were a different group of patients. They
16 were a more active group of patients at the point that they
17 were randomized into the study.

18 Q. So let's turn to JTX 2235, which is the Kappos 2006.

19 Dr. Greenberg, what is JTX 2235 shown on DDX 1100,
20 Slide 70?

21 A. So this is an abstract that was published in the Journal
22 of Neurology in 2006, Supplement 2, and it's entitled "Efficacy
23 of a Novel Oral Single-Agent Fumarate, BG-12, in Patients with
24 Relapsing-Remitting Multiple Sclerosis: Results of a Phase 2
25 Study."

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1 Q. And was this abstract published at the journal -- for the
2 Journal of Neurology meeting for the 16th Meeting of the
3 European Neurological Society on May 27th through 31st?

4 A. Yes, this is the abstract that correlates with that
5 meeting.

6 Q. And who is the first named author?

7 A. Dr. Kappos.

8 Q. And who sponsored the study?

9 A. This is the study as sponsored by Biogen Idec and
10 Fumapharm AG.

11 Q. And when was it published?

12 A. In 2006.

13 Q. And what does the Kappos 2006 abstract describe?

14 A. So the Kappos 2006 abstract describes the results of this
15 Phase 2 study that included four arms: a placebo and three
16 treatment arms of BG-12.

17 Q. And what does the abstract say about the results of the
18 Kappos Phase 2?

19 A. So it notes that "BG-12 at 720 milligrams a day
20 significantly reduced the mean number of new gad lesions (the
21 primary end point) compared with placebo." And goes on to say
22 "BG-12 significantly reduces brain lesion activity in a
23 dose-dependent manner as measured by MRI."

24 Q. And so when it refers to brain lesion activity, that's the
25 Gd-enhancing lesions?

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1 A. Yes.

2 Q. And, again, what does it mean when the abstract describes
3 the activity in a dose dependent manner?

4 A. So reading in an abstract like this, which the study had
5 indicated there were going to be multiple dosing arms tested
6 going from low dose to high dose -- in this case, 120 to
7 720 milligrams a day. When it describes a dose-dependent
8 manner, a skilled artisan takes away that, as the dose goes up,
9 incremental increases in efficacy occur. And at this point,
10 the highest dose that was used, 720, met its primary end point.

11 Q. Now, are you aware of Biogen's argument that, because
12 480 milligrams is numerically closer to 360 milligrams than
13 720 milligrams, that you would not have reasonable expectation
14 of success that the 480-milligram dose would work?

15 A. I'm aware of this.

16 Q. Did you prepare a slide to discuss or explain this
17 argument?

18 A. Yes.

19 Q. Well, do you agree with the argument?

20 A. I don't.

21 So if I may?

22 Q. Yes, please. Why not? Yes.

23 A. Okay. So when talking about dose-response curves, what's
24 being suggested by Biogen in response to our argument is what's
25 known as a linear dose-response curve -- it's shown on the

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1 left -- where, for every milligram I add, I get more efficacy.
2 And it's -- what I sometimes worry my patients will do, well,
3 10 milligrams was good, 20 will be better. And they increase
4 the dose. And that's usually not a good idea across the board.

5 But in terms of what we're talking about today,
6 immunologically, the dose-response curve -- and for many
7 conditions -- is not linear. That when you're dosing a
8 medication, there comes a point where each additional milligram
9 of the medication no longer adds any efficacy; you only add
10 risk of side effects.

11 And the reason for this has to do with the target of the
12 medication. So to bring it home to dimethyl fumarate, the
13 target of the medication is the immune system. The target, as
14 understood by skilled artisans, as presented by Dr. Kappos in
15 the presentation, is this Th1 to Th2 shift.

16 Once I reach a dose on this curve that has shifted the
17 immune system, I don't need to shift any more. I have achieved
18 a dose that will lead to a clinically meaningful response in a
19 significant proportion of the population. It doesn't have to
20 be all the population because you have to balance the risks.

21 To get that very last patient into remission, if you had
22 to pick a dose that subjected all the other patients to side
23 effects with no additional benefit, you would not move to the
24 right on this curve. You would sit squarely in a place where
25 you had turned the corner and were seeing efficacy.

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1 Since, in multiple sclerosis, we don't have a blood test
2 to measure the immune system activity to pick where we are on
3 this dose-response curve, we use the clinical trial data. We
4 look for doses in the art to tell us at what range do you turn
5 the corner, do you get to the flat part of the curve?

6 Even without Kappos, if we just looked to Schimrigk, we
7 knew that, between 360 and 720, we were on that point of the
8 curve. Kappos confirms that. Kappos goes further in the study
9 to show us 360 to 720 work.

10 And if we take at its core that pretty much everybody was
11 accepting psoriasis and multiple sclerosis shared an
12 immunopathology, we have a wealth of psoriasis literature to
13 say we meet the clinical end point we want at this point of the
14 curve at 480.

15 And so whether 480 is closer to 360, that is
16 mathematically correct, but the fact that it would teach a
17 skilled artisan to go over here on the curve is incorrect.

18 Q. Thank you.

19 MS. BLOODWORTH: Your Honor, this is kind of a good
20 stopping point. Is that okay?

21 THE COURT: Yes. I agree. I agree.

22 Can you estimate how much longer you have with
23 Dr. Greenberg tomorrow?

24 MS. BLOODWORTH: I believe we will probably go for
25 about an hour and a half.

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1 THE COURT: Okay. And then on cross-examination, the
2 rest of the day, or might we get through another witness?

3 MR. FELDSTEIN: We might get through another witness.
4 And I think we may need to discuss with Mylan's counsel --

5 THE COURT: I should have said this is Wednesday,
6 not --

7 MR. FELDSTEIN: Yeah, Wednesday. You're right.

8 We have some scheduling issues with one witness, and
9 we need to make sure that we get him on the stand before he has
10 to go back.

11 THE COURT: Right. Well, as I've said before, if we
12 have to interrupt, we'll do it to make that happen.

13 MS. BLOODWORTH: We'll discuss that, sure.

14 THE COURT: Okay. Are you up for a question?

15 MR. MONROE: I just wanted to make sure on the --
16 this is Tuesday. And tomorrow we were supposed to be off. I
17 just want to make sure we're talking about Thursday now. Is
18 that correct?

19 THE COURT: That's right.

20 MR. MONROE: I just wanted to make sure.

21 THE COURT: It's 5:00. It's about 100 degrees in
22 here. You can tell me what day it is.

23 Yes, that's right. So we're not in here tomorrow.
24 We are back here on Thursday. Very good. I'll be here.

25 Thank you, Dr. Greenberg. You're free to step down.

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1 And we will get back to you all with the status of
2 the temperature in here. And if we're like this again when we
3 resume, you don't have to keep your jackets on. This is pretty
4 horrible. So we'll see what we can do. Okay?

5 Thank you.

6 Court stands adjourned.

7 Oh, and we're going to resume -- when we do resume,
8 it's 8:30. Okay? Very good.

9 (Proceedings concluded at 4:59 p.m.)

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CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on February 4, 2020, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 4th day of February 2020.

/s/Cindy L. Knecht

Cindy L. Knecht, RMR/CRR
Official reporter, United States
District Court for the Northern
District of West Virginia